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APPLIED ANATOMY OF THE FEMORAL VEIN AND ITS TRIBUTARIES

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FOR a variety of reasons, the femoral vein has become the object of frequent surgical attack, yet the arrangement of the trunks entering this vessel and the pathways for its collateral circulation are not well known. Chief among the present indications for operation on the vein is the presence of venous thrombosis in the leg or thigh. The anatomy of the femoral vein will here be considered in special reference to its surgical interruption for this disease to prevent the transport of thrombotic emboli.

The usual textbook description of the femoral vein lists its tributaries as the saphenous and the deep femoral veins, with only a few additional minor muscular tributaries. Yet, at operation, it is apparent that several large veins enter the femoral under the deep fascia. The surgeon's problems are: first, to determine, within the limited exposure of his incision, which of these is the deep femoral vein and which other vessels, whose more transverse course in the upper thigh are less likely to transmit either the thrombosis itself or an embolus, from the lower thigh; second, to identify possible collateral channels of the femoral vein of a size sufficient to carry emboli around his interruption of the main trunk; third, to know where best to place his ligature with reference to the main anastomotic pathways from the femoral vein to the pelvic veins.

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OBSERVATIONS

To shed light on these questions, we have examined the arrangement of the femoral venous system in 61 extremities in the dissecting room. Previous anatomic investigations, while excellent in many ways, still fail to answer our problem satisfactorily. These previous investigations and the results of the present study will be considered under the separate headings of anomalies of the femoral vein proper, tributaries of the femoral vein, its collaterals, and finally, anastomotic pathways from the thigh.

A glance at the accompanying diagrams impresses one with the great variations that exist, both in regard to the pattern of the venous channels, and the levels of their termination in the femoral vein. Moreover, the vessels not only vary greatly from one individual to another, but also often fail to show a bilateral symmetry in the same individual. In the diagrams, the terminations of all the large venous trunks have been recorded; and care has been taken to locate accurately to scale, the vertical relation of these levels to the inguinal ligament. It is probable that in most live individuals, the ligament would be stretched downward 1 centimeter or more, below its position in the thin cadavers studied.

1. *Anomalies of the femoral vein proper.* The only gross anomaly of the femoral vein proper encountered in this study was the termination of this vessel in the hypogastric (Fig. 9),

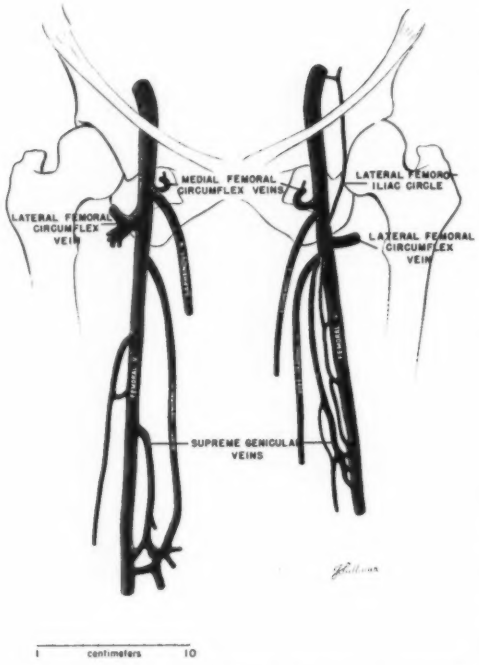

Fig. 1. A venous arrangement showing an unusually large communication of the lower right deep femoral with the femoral vein below (incidence 10%). There are several femoral collaterals, all ending below the deep femoral termination. In the left limb, a lateral femoroiliac circle extends from the deep circumflex iliac vein to a femoral collateral. Large supreme genicular veins are present.

with a rudimentary external iliac vein. The author has not seen any record of such an anomaly in the literature. Other anomalies, that are probably more common though not met with in this study, are mentioned by Testut, namely, a persistent posterior course of the popliteal vein which runs in the thigh for a variable distance before perforating the adductor magnus to rejoin the artery, and, seen less often, a course of the vein beside the sciatic artery to enter the pelvis with it. "Doubling" of the femoral vein was encountered twice in this study and will be considered in the section on collaterals.

The relation of the femoral vein to the artery was found to be variable. Instead of lying posterior to the artery, it was occasionally found anterior, or lateral. In one instance a medial femoral circumflex artery arising in the pelvis lay in front of the vein. From a larger series of 250 subjects Hovelacque gives the following statistics: The vein lay anterior to the artery seven times, lateral four times; it described an arcade about the artery three times.

The relationship of the deep femoral vein to the corresponding artery was likewise variable.

No mention will be made here of the mode of branching of the femoral artery. This subject has little bearing on the present problem and has been adequately covered by other workers.

2. Tributaries of the femoral vein. The vessels draining directly or indirectly into the femoral vein correspond roughly in source to the distribution of the femoral arterial channels. It will be recalled that the femoral artery gives off three subinguinal branches to superficial areas—the superficial circumflex iliac, epigastric, and external pudendal arteries; then a deep femoral artery, and directly or from this latter vessel—medial and lateral femoral circumflex arteries. A deep external pudendal branch comes from the femoral artery or from the medial femoral circumflex. The medial femoral circumflex artery has a horizontal course, running deeply through the upper adductor region to the upper posterior thigh. The lateral femoral circumflex vessel has an upper branch which ascends, a transverse one which follows a horizontal course around the upper end of the femur, and a descending ramus which courses between the rectus femoris and vastus lateralis muscles to the lateral side of the knee. The deep femoral artery has a distinctly distal course, medial to the femur, and anterior to the upper adductor muscles and in turn to the adductor magnus; it gives off two to five branches termed the perforating arteries, the last of which lies just above the opening in the adductor magnus for the femoral artery. The lowest branch of the femoral artery is the supreme genicular, arising in the lower adductor canal and bifurcating into the musculoarticular artery, which supplies the knee joint, and the saphenous artery. Finally, a number of unnamed branches arise both within the trigone and in the ad-

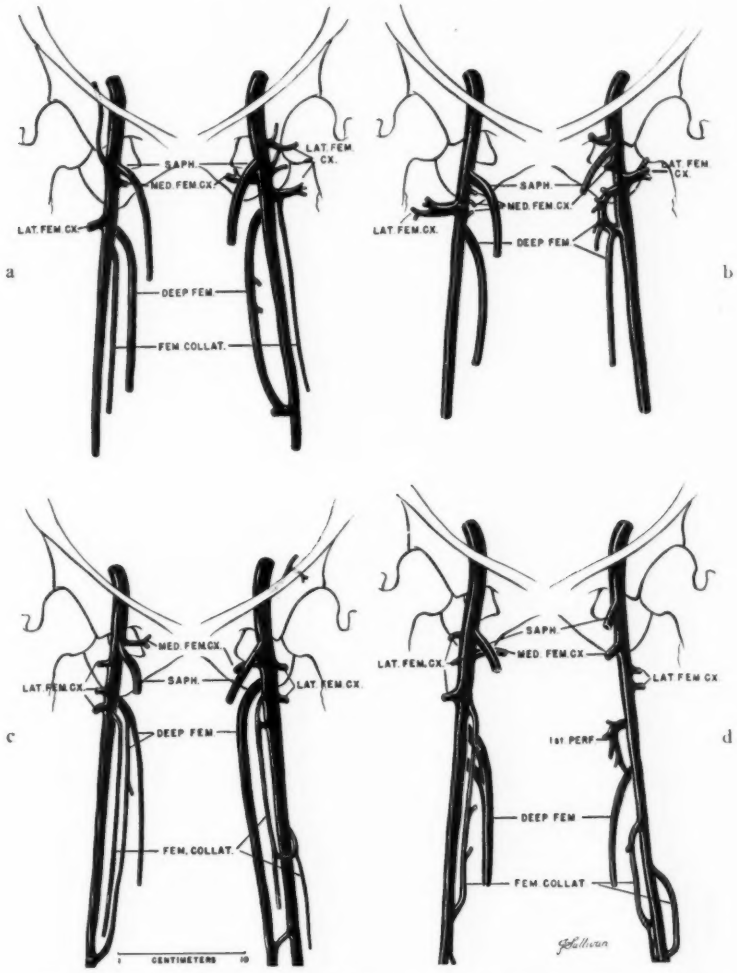

Fig. 2. Varieties of communications between the deep femoral and femoral veins. In a and c, the lower deep femoral has gross communications with the femoral. In c, left, the deep femoral is doubled. In b and d, are varieties of communications of the upper deep femoral vein.

ductor canal, with rather transverse courses to the contiguous muscles.

Returning to our observations on the veins, it was apparent that the venae comitantes of the musculoarticular and saphenous arteries did not often join to form a *supreme genicular vein*. When this did occur, the resulting vessel was slender and paralleled the femoral vein for long distances, appearing as a collateral vein, until it emptied into the femoral, or terminal deep femoral, vein (Figs. 1, 3).

Our observations go even farther than those of Charles and his associates in pointing to the infrequency with which the *deep femoral* receives the circumflex femoral veins. In a larger series than the present, namely 165 extremities, these workers found that the circumflex veins emptied wholly into the femoral

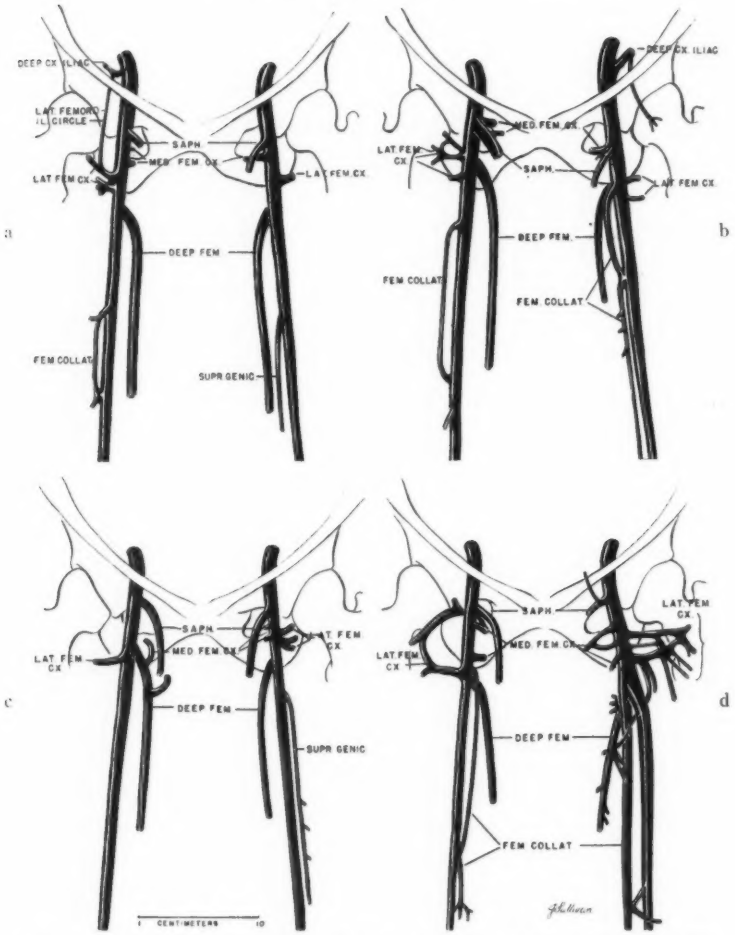

Fig. 3. Varieties of collateral femoral veins. None extend much higher than the deep femoral ending. In a and c, apparent collaterals are actually the supreme genicular veins. In d, there is a "double" femoral vein.

vein proper in 76 per cent. In our study the deep femoral received the medial femoral circumflex but once, the lateral, five times. Moreover, the venae comitantes of the first or second perforating arteries may likewise enter the femoral (Fig. 2, b, d). We may therefore define the deep femoral vein as the vessel resulting from the fusion of the lower perforating veins, usually receiving the upper perforating veins, and occasionally the circumflex femoral veins.

The deep femoral vein (Figs. 1, 2) is almost always the most inferior of the large venous channels entering the femoral, though a low lateral femoral circumflex vein or an exceptional collateral may enter at this level. The deep femoral vessel terminated in the femoral vein at an average of 8 centimeters below the inguinal ligament. The shortest distance was 5 centimeters, the longest 11.5 centimeters. There was only approximate correspondence with the height of the individual. Moreover, while

bilateral equality of level was the rule, exceptions were found varying up to 3 centimeters.

In 6 instances the inferior end of the deep femoral vein showed a large communication with the femoral just above the adductor opening. It is obvious that such a connection must be taken into account as a possible pathway for extension of a thrombus or an embolus, from a process in the popliteal or lower femoral vein. In 3 instances (Fig. 2, b, d) the deep femoral terminated by 2 mouths entering the femoral vein. Such a communication would again be of significance in an attempted interruption. In 3 cases the deep femoral showed doubling.

The *lateral femoral circumflex vein* usually emptied into the femoral above the deep femoral vein. Often the tributaries corresponding to the 3 main divisions of the artery remained as separate trunks, so that 2 or 3 lateral femoral circumflex veins were not uncommon, and the lowest of these sometimes ended in the deep femoral.

The *medial femoral circumflex vein* was ordinarily the highest of the large veins to enter the femoral, ending at or above the level of the saphenous termination. It was usually single. When it terminated as two veins, the upper occasionally received the small deep external pudendal vein. In most instances, however, this vein ended directly in the femoral.

The superficial subinguinal veins, including the *superficial epigastric*, *circumflex iliac*, and *external pudendal* veins, ended as small vessels in the terminal *saphenous*, or occasionally directly in the femoral vein immediately above the saphenous. Little additional need be said of the saphenous vein. Its anatomy has been covered in a previous report (4). Its termination in the femoral is of course easily seen, lying as previously reported, at an average of 1.7 centimeters below the pubic tubercle; which corresponds quite well to a point four centimeters below the inguinal ligament as measured in the present study.

Additional veins terminating in the femoral were irregularly placed and generally small, tributaries from the muscles as well as collateral veins and circles to be described in the following.

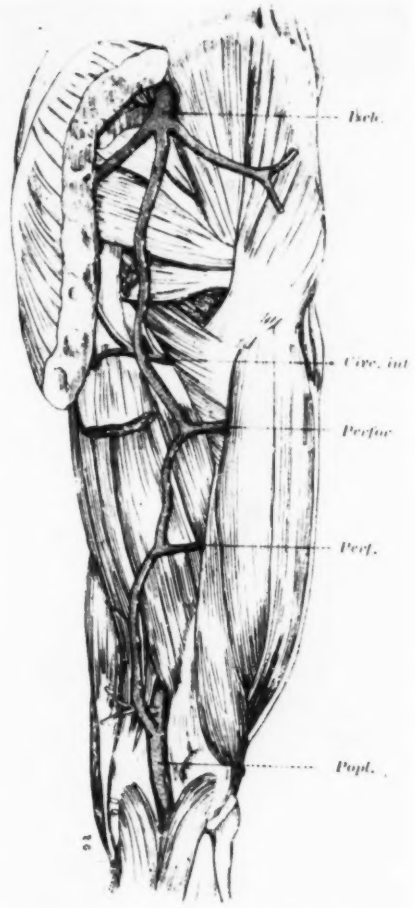

Fig. 4. The collateral venous plexus in the posterior thigh. The deep veins were injected after the femoral was tied at the inguinal ligament. (From Hovelacque.)

3. Collaterals of the femoral vein. Clinically, the term collateral is used to denote any anastomotic channel. Anatomically, the word is more limited, and it may be well to define it now, in order to differentiate collaterals from the "venous circles" to be mentioned in the next section. The characteristics of a true collateral have been summarized by Hovelacque. It is a vessel that runs parallel to a more important vein, and communicates with the major vein at its two extremities. In this

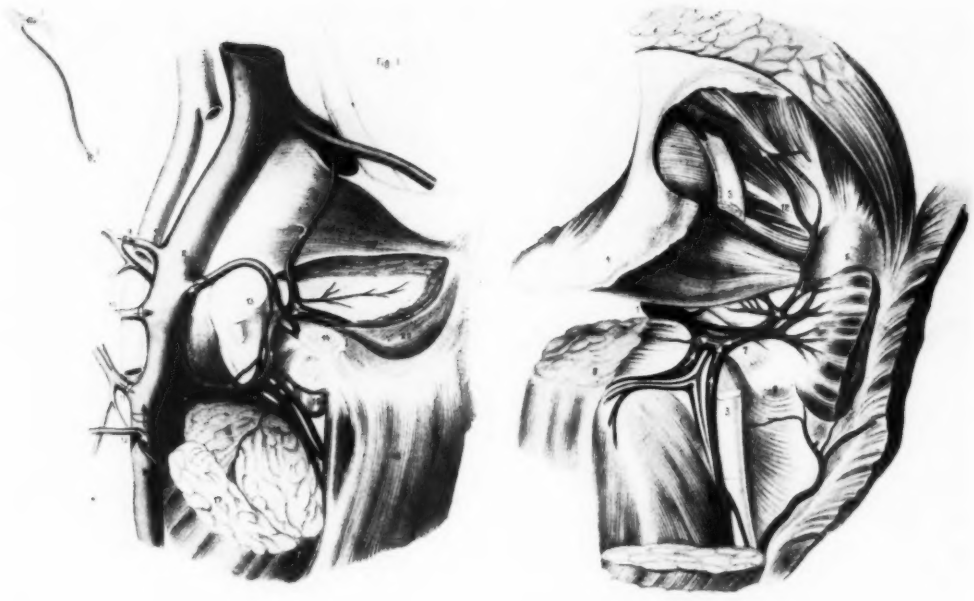

Fig. 5.—"Venous circles." On the left, the medial femoral circumflex vein inosculates with the obturator, and on the right, its posterior portion enters the inferior gluteal. Arrows indicate valve orientation. (From Braune.)

way it extends from one segment of the parent vein; i.e. a portion between two valves, to another segment. Valves are usually present in the collateral, and are always directed centripetally. The rôle of collaterals is denoted in their being termed *canaux de sûreté* (Verneuil, 5). Their functions are to receive overflow from the principal vein—preventing stasis, equilibrating pressures, and relieving valves in the main trunk from excessive strain. Picqué and Pigache, finding more and larger collaterals of the femoral vein in the newborn, thought them to be vessels in a state of "regressive atrophy." While this may be true, it hardly explains their occurrence, although it may prove that the body economy may not demand their persistence in their original size.

Langer had insisted that quite constantly two or three collateral femoral veins are present. From the present study one may agree that at least one such vessel is almost always present, though so small as to be easily overlooked. The form of collaterals coincides quite well with the descriptions offered by Langer, and by Picqué and Pigache. The vessels are generally narrow, longitudinally disposed channels, originating in the popliteal, or the lower femoral veins. They are remarkable for the limited number of their communications with the femoral and for their termination in the lower levels of that vein. It is rare to find them continued above the ending of the deep femoral vein. Moreover, they receive but a few tributaries, which are small veins from the muscles. The supreme genicular vein often ascended for long distances and appeared as a collateral vessel. This is also mentioned by Hovelacque, who adds that an articular vein from the popliteal region may also constitute a collateral. "Insular" formation by division of the femoral, and fusion at a higher level has been observed.

Great enlargement of a collateral to give "doubling" of the femoral vein was encountered only twice. One may agree with Picqué and Pigache that even in these instances each

of the pair of veins receives the tributaries characterizing the usual femoral vein, and a collateral, respectively. Moreover, a doubling of the femoral vein was never seen in its uppermost portion.

Mention must here be made of the anastomotic chain in the posterior thigh effected by the junction of the perforating and both circumflex femoral veins with the popliteal below and the inferior gluteal above (Fig. 4). The pathway thus formed constitutes an additional collateral system for the femoral vein. The inconstancy of its popliteal connection tends to reduce its usefulness. Moreover, its valves are arranged as in a "venous circle," that is, for flow to each segmental parent trunk, rather than for an uninterrupted upward flow. Apparently, however, the veins of this pathway dilate easily, rendering the valves incompetent, for it is shown to be the most important anastomotic pathway in interruptions of femoral vein at any level (6).

It may be well to note that two other veins beside the femoral assist in drainage from the upper thigh: namely, the inferior gluteal and the obturator. Their direct drainage is so limited, however, that they perform this function mainly through their anastomoses with tributaries of the femoral vein. We may now consider in more detail the nature of these and other anastomoses at this level.

4. Anastomotic pathways from the thigh. It will be recalled that true collateral vessels were found anastomosing with the femoral vein, but reaching no higher than the deep femoral termination. Above this point only occasional collaterals exist, in the form of arcades along the constituent trunks of the medial or lateral femoral circumflex veins. Only exceptionally are the anastomoses found valved for centripetal flow from the femoral to the iliac veins. Instead, these communications are valved so as to form channels denoted by Braune as "venous circles." In these (Figs. 5 and 6) the valves are so oriented that blood may flow into each of the veins, or vein segments, which the circle connects, but not from one level to the other. In order to function as collaterals, it is therefore necessary that such vessels undergo a preliminary dilatation to render the valves incompetent.

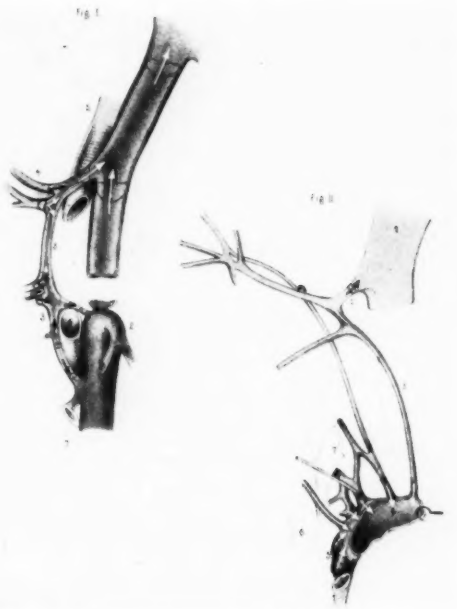

Fig. 6. The lateral femoroiliac circle. A deeper component is shown in the lower right. Arrows indicate valve orientation. (From Braune.)

The largest of the venous circles encountered was the bifurcated pathway constituted by the inosculation of the medial femoral circumflex vein, with the obturator and inferior gluteal veins (Figs. 7, 8, 9). The prime importance of these pathways has been indicated by the injection experiments of several workers (2, 5, 6, 10). These are not only the largest of the anastomoses from the femoral vein upward, but moreover, as Braune pointed out, valves may be lacking in the medial femoral circumflex vein, allowing an immediate centripetal flow (Fig. 8, a, d).

Accessory routes in this vicinity, probably arranged as venous circles, are the communications between the deep external pudendal, and the internal pudendal and obturator veins, as well as with the deep dorsal vein of the penis. The latter in turn empties into the vesicoprostatic plexus within the pelvis. Here, experiments (1, 6) indicate that the sacral veins, and the entire vertebral "system" of veins, aid the iliac in carrying the blood upward.

Fig. 7. Varieties of valve arrangement in the gross anastomotic channels of the femoral vein. The veins collateral to the lower femoral in a are valved centripetally. The veins extending from the upper femoral to the iliac veins are valved toward each parent trunk. In both a and b, the anastomosis from the medial femoral circumflex to the inferior gluteal is incomplete. In b, the lateral femoroiliac circle is incomplete.

In lateral relation to the femoral vein lies a venous circle described by Braune as the circumflex iliac circle, and denoted here as the lateral femoroiliac circle (Figs. 7, 8, 9). This vessel extends usually from the lateral femoral circumflex vein, or the femoral above this level, to connect with the deep circumflex iliac vein. Connections with the superficial circumflex iliac vein were not uncommon, and occasionally, as Braune shows, the circle may be made up of several vessels, some superficial, others deep to the femoral artery or nerve (Fig. 6). The valves of this circle are rather perfectly oriented toward each of its two ends. This fact, as well as its usual small caliber, limits its immediate utility as an anastomotic path. Yet it would seem that this vessel deserves a place in our textbooks and in our thinking. It was found in the present study in 17 limbs, and it is the writer's impression that some small vessel or vessels representing it may be even more often observed. Moreover, it is not always small for, in one case (Fig. 9), it attained a diameter of 1 centimeter.

It should be mentioned here that aside from the deep anastomoses mentioned, there exists a series of superficial venous circles connecting the femoral with other veins. Reference is made to the upper end of the saphenous and its tributaries, which, when dilated, furnish large anastomoses from the femoral to the veins of the trunk and axilla.

SUMMARY AND CLINICAL CONCLUSIONS

The femoral vein may vary in its relation to the femoral artery, occasionally lying anterior or lateral to that vessel. Rarely it may course for a variable distance in the posterior thigh. Collaterals of the vein are extremely frequent in its lower course, and occasionally a collateral may be large enough to constitute a doubled femoral vein.

The deep veins of the thigh join the femoral as several trunks rather than as a single one. The deep femoral vein is formed by a fusion of the venae comitantes of the perforating arteries, and only seldom receives the lateral or medial femoral circumflex veins, which enter the femoral vein separately. Each of the circumflex veins may exist as two or three vessels. The deep external pudendal vein may join the medial femoral circumflex, or the femoral vein directly.

In identifying the tributaries of the femoral vein, the level of termination of each vessel is of some value. The deep femoral vein enters the femoral vein at an average of 8 centimeters, or four finger-breadths below the inguinal ligament. The lateral femoral circumflex vein enters the femoral above this point, and the medial femoral circumflex at a still higher level—approximately that of the saphenous termination. The inguinal ligament used as a point of reference here is not usually identified during life; and the crease of the groin may be deceptive, since it descends with an increase of bodily fat. The pubic tubercle is a better landmark. It lies about 2 centimeters below the part of the ligament referred to in this study.

The lower deep femoral vein was found to have a gross communication with the femoral in 10 per cent of our limbs. There is thus great danger of extension of a thrombus along the deep vessel when the popliteal or lower femoral vein is thrombotic. This fact suggests that the femoral should always be interrupted *above* the termination of the deep vein. The other veins entering the femoral have fewer possible connections with a process at the popliteal or lower femoral level. It is only when thrombosis exists in the upper part of the femoral vein that interruption need be done above the ending of the femoral circumflex veins.

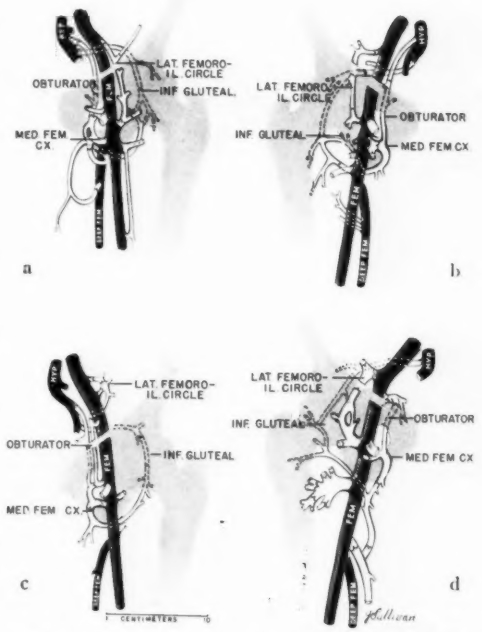

Fig. 8. Varieties of valve arrangement in the gross anastomotic channels from femoral to iliac veins. Exceptional arrangement allowing uninterrupted centripetal flow is present in the medial femoral circumflex veins in a and in d, and in the lateral femoroiliac circle in b, in c, and in d.

Two other factors may influence the choice of the level for interruption of the femoral vein. They are the amount of the blood mass impeded, and the anastomotic channels available, at various levels.

Three levels at which it is practicable to divide the femoral may be considered in this connection:

1. *Below the termination of the deep femoral vein.* This ordinarily gives rise to little or no

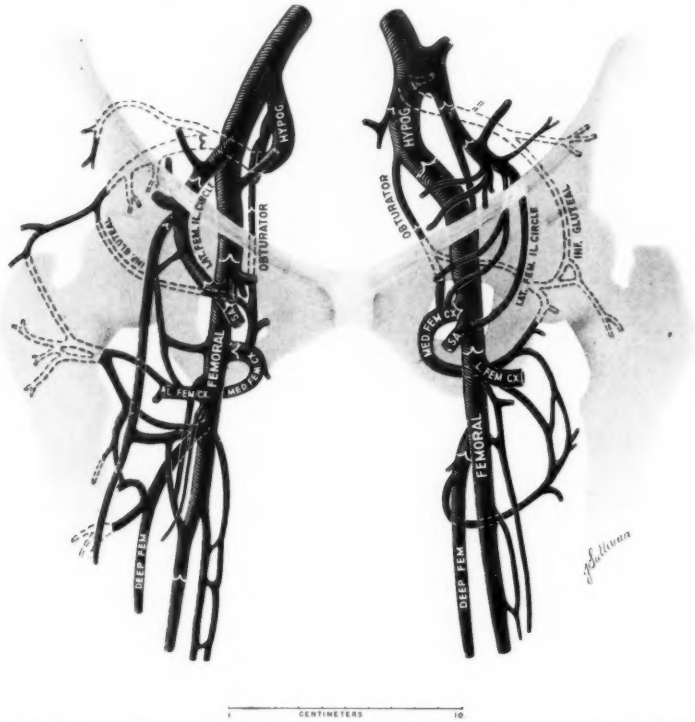

Fig. 9. Gross anomaly of the femoral vein, and valve arrangement in the main anastomotic channels from femoral to iliac veins. The left femoral enters the pelvis normally, but terminates in the hypogastric vein. A small external iliac vein is present. An unusually large lateral femoroiliac circle is present in the right thigh. On both sides this structure is valved centripetally (unusual). The circles formed by the medial femoral circumflex and obturator and gluteal veins are valved toward each parent trunk.

venous obstruction. Comparatively little blood mass is impeded, and the deep femoral vein constitutes a good anastomotic channel. Collateral femoral veins when present are likewise good anastomotic pathways, because they too are valved for centripetal flow. They suffer from their usual failure to reach upward high enough to cross this point of vein division. Interruption at this level will fail to close off pathways for embolism in 10 per cent of individuals.

2. Above the deep femoral, but below all or the major number of lateral and medial femoral circumflex channels. This interruption has the merit of not trapping the large amount of blood carried by the circumflex or the saphenous veins. Moreover, the saphenous is subjected to minimal dilatation. Interference with blood flow nevertheless may be considerable, because of the usual paucity of gross anastomoses across this level. The largest path available is formed by the chain of veins in the posterior thigh contributed to by the deep femoral vessels and ending in both femoral circumflex vessels, and the inferior gluteal, above. The valves in these veins are oriented toward each parent trunk, rather than in an uninterrupted upward direction, and the lower parts would require a period of venous dilatation before their valve resistance would be obviated.

3. Above the level of the saphenous and both femoral circumflex veins. This is an alternative position for interruption above the deep fem-

oral termination. In comparison with the previous level mentioned, a larger mass of blood is trapped below the ligature, and there is the added disadvantage in the inability of the saphenous to empty itself through its communications except after dilatation overcomes its valve resistance. Theoretically this should lead to the highest incidence of varicose widening of the saphenous.

The advantage of using this level lies in the availability of gross anastomotic routes leading upward to by-pass the interruption. The largest of these is a "venous circle" comprised by the medial femoral circumflex vein inosculating with the obturator and inferior gluteal veins. Accessory channels medial to the femoral vein, consist of the deep external pudendal vessel communicating with the dorsal vein of the penis and the internal pudendal, and thus with the pelvic veins. Laterally there is often present a "lateral femoroiliac circle," connecting the femoral to the deep circumflex iliac veins.

The routes mentioned, as well as the superficial anastomoses leading from the saphenous to the veins of the trunk and axilla, are most often valved as "venous circles," that is, toward each parent trunk, rather than from the femoral upward. This renders the anastomoses unusable as collateral channels until they have undergone dilatation with resulting valvular incompetence.

Femoral division at this level, often produces much more cyanosis and edema than division at either of the two other levels mentioned. Nevertheless, in the few cases in which one of us (E. A. E.) has divided the femoral vein at this level, the symptoms have subsided in a few hours or days, presumably when dilatation of the anastomotic channels has become adequate.

It would be well for surgeons to record carefully the exact level used in operations on the femoral vein, based upon a more exact localization than heretofore used. In this way, optimal levels of interruption may ultimately be learned.

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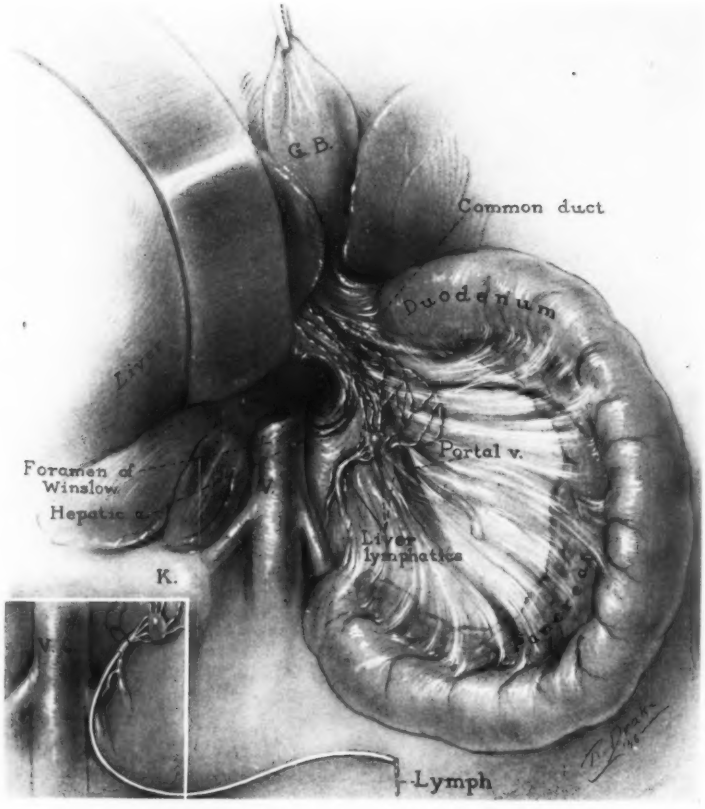

Fig. 1. The extrahepatic lymphatics in the dog.

Lymph from Liver and Thoracic Duct.—*James C. Cain, John H. Grindlay, Jesse L. Bollman, Eunice V. Flock, and Frank C. Mann.*

LYMPH FROM LIVER AND THORACIC DUCT

An Experimental Study

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SINCE 1894, when Starling showed that ligation of the inferior vena cava above the openings of the hepatic veins caused marked increase in the flow of lymph in the thoracic duct, it has been presumed that the liver is the site of origin of a major portion of the lymph present in the thoracic duct. Markowitz and Mann, however, in 1930 noted that the flow of lymph in the thoracic duct after hepatectomy was diminished only slightly, if at all. Their dogs, after hepatectomy, made the usual response to administration of lymphagogues, with great increase in the flow of lymph in the thoracic duct.

Few attempts have been made to study uncontaminated lymph from the liver; most investigators have cannulated the thoracic duct in the neck and indirectly have estimated the flow of hepatic lymph. The purpose of this investigation was to compare, in trained dogs, the rate of flow and the composition of hepatic lymph obtained directly from a cannula in the lymph vessels of the liver with similar values for lymph obtained from the thoracic duct.

MATERIALS AND METHODS

Dogs weighing 12 to 26 kilograms were used in this investigation. Except in the case of a few studies made with the animals under anesthesia, the dogs were trained to stand while the lymph was collected. The best preparations were in the young dogs. Approximately a third of the operations resulted in satisfactory preparations as evidenced by a free and uniform flow of lymph. In this paper the term "fistula" will be used to describe the condition after this operation. The lymph was collected continuously for as long as 55 hours from the liver and 8 days from the thoracic duct.

The cannula used consisted of capillary-sized plastic tubing that extended several inches beyond its exit through a tiny stab wound in the body wall. In these investigations polyvinyl resin tubing (transflex,[1] size 24) was used. The tubing was flexible, quite elastic, transparent and smooth-walled; it could be cut with a knife or scissors as easily as rubber; it did not crack or tear and it could be sterilized by boiling. Small-sized tubing was practically inert biologically although it was found that enough plasticizer is present in larger masses of polyvinyl resin substances to cause slight irritation. Probably the most valuable characteristics of this tubing were its flexibility and its tendency to cause only slow clotting of lymph within it.

The end of the tubing which was placed in the lymphatic was cut on a bevel of approximately 45 degrees. The exposed surface of the lymphatic to be cannulated was stripped clean and a tiny hole was made in the presenting surface. While tension was placed on the lymphatic and the hole was held open with a fine seeker of blue glass, the beveled tip of the transflex tube was inserted into the lymphatic. Frequently the first valve of the lymphatic was ruptured or evaded by the glass seeker, in which case it was possible to insert a longer length of tubing in the lymphatic. After the tube was in place and the glass seeker withdrawn, a previously placed ligature was tied about the lymphatic and tubing.

In the dog the lymphatics emerge from the hilum of the liver and, anastomosing freely

From the Divisions of Medicine and Experimental Medicine, Mayo Foundation.

Abridgment of a thesis submitted by Dr. Cain to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

Presented in the Forum on Fundamental Surgical Problems before the Clinical Congress of the American College of Surgeons, Cleveland, Ohio, December 16 to 20, 1946.

[1]The transflex tubing used in this study was furnished through the courtesy of the manufacturer, Irvington Varnish and Insulator Co., Irvington, New Jersey.

TABLE I.—RATE OF FLOW OF LYMPH IN DOGS, CUBIC CENTIMETERS PER 10 MINUTES

Description of dogs	Determined alternately				Determined simultaneously			
	Liver		Thoracic duct		Liver		Thoracic duct	
	Range	Mean	Range	Mean	Range	Mean	Range	Mean
Anesthetized	1.5–5.8	2.96	3.7–10.9	7.1	1.6–5.8	2.80	4.3–15.2	8.03
Trained, not anesthetized	0.3–5.2	1.83	0.8–14.0	3.77	0.6–0.9	0.72	2.8–4.5	3.3
All dogs		2.26		4.6		2.35		7.05

over the surface of the gastrohepatic ligament, run caudally to the hepatic lymph node adjacent to the portal vein (Fig. 1). These vessels and the lymph within them are transparent and almost colorless. The lymphatics are thread-sized, have extremely thin and delicate walls and possess valves at frequent intervals. Emerging from the hepatic lymph node and passing dorsally toward the vena cava are a few efferent lymphatic trunks, one of which is usually larger than the others. This largest efferent lymphatic was the one that was cannulated. Occasionally we have seen 2 or even 3 hepatic lymph nodes with variations in the number and anastomotic arrangement of the efferent trunks.

As previously indicated in order to obtain virtually all the hepatic lymph a mass ligature was placed around the entire efferent lymphatic region after the largest vessel had been cannulated. In order to block the few small lymphatics which enter the hepatic node from the duodenum and pancreas, one or more mass ligatures were placed about the afferent lymphatics at the caudal end of the hepatic lymph node.

In a few early studies the thoracic duct was cannulated at the usual site, where it joins the left subclavian vein. When the duct was cannulated near its origin a greater flow of lymph for a longer time was obtained. Recently we have cannulated the duct above the diaphragm where usually it is a single vessel lying behind the descending thoracic aorta. Smaller lymphatic vessels of the retro-aortal areolar tissue were occluded by a mass ligature of this region. Since there are no valves in the thoracic duct, the plastic tubing could usually be threaded down the duct until its tip was in the cisterna chyli.

RESULTS

The normal rate of flow of lymph in the thoracic duct has been variously estimated as from 1.24 to 27.0 cubic centimeters, with an average of 4.0 cubic centimeters, per 10 minutes. Estimation, by direct measurement, of the total quantity of lymph produced by the liver has not been made previously. The normal rate of flow of lymph in both the thoracic duct and the liver, as determined under various experimental conditions by use of the technique described in preceding paragraphs, is shown in Table I. There is great variation in range of normal rate of flow of lymph both from the liver and the thoracic duct. The rate of flow was increased after anesthesia with ether. Under the conditions of these studies, the liver contributed approximately a fourth to a half of the lymph in the thoracic duct. The rate of flow was apparently greater in large, than in small dogs and in young, than in old dogs. The state of hydration and stage of digestion were also important factors which affected the rate of flow.

The protein content of lymph from different parts of the body varies. Lymph from the leg contains, according to Drinker and Yoffey, 0.5 to 1.5 grams of protein per 100 cubic centimeters. In the studies reported herein, the value for protein in lymph from the thoracic duct was about half the value for that in blood plasma. The value for protein in hepatic lymph was usually approximately five-sixths the value of that in blood plasma. Animals with fistulas either of the lymph vessel of the liver or of the thoracic duct soon gave rather marked evidence of hypoproteinemia. This occurrence is easily understood when it is remembered that, in 24 hours, approximately 280 cubic centimeters of lymph will drain from a hepatic fistula and that approximately 700 cubic centimeters will drain from a fistula of the thoracic duct. There is some evidence that most of the protein in hepatic lymph is newly formed. Loss of weight is conspicuous in dogs with either type of fistula.

That glucose, when injected intravenously, acts as a lymphagogue, as indicated by an in-

crease in the rate of flow of lymph in the thoracic duct, has been known for many years. It had been assumed, under these circumstances, that most of the increase in quantity of lymph originated in the liver. In the studies reported herein determinations were made of the effect of intravenous injection of 20 per cent solution of glucose at a rate of 0.5 gram of glucose per kilogram of body weight, into 12 dogs with a lymphatic fistula of the liver and into 8 dogs with a fistula of the thoracic duct. In every instance an increase in the rate of flow of lymph from the liver and thoracic duct occurred. In both groups the rate of flow began to increase during the first 10 minutes after administration of glucose and reached a peak within 30 minutes. On the average, the increase from the hepatic fistula was 68 per cent and that from the fistula of the thoracic duct was 75 per cent. The difference between these two percentages is probably not significant. In one dog with a fistula of the thoracic duct, injection of 50 per cent solution of glucose at a rate of 1.5 grams of glucose per kilogram of body weight was followed by an increase of 350 per cent in the rate of flow of lymph.

Studies were made to determine the relative changes in the sugar content of blood plasma and of lymph of fasting dogs after intravenous injections of glucose (Fig. 2). In fasting dogs before injection of glucose, the sugar content of lymph from the liver and thoracic duct was, on the average, about 10 to 20 milligrams per 100 cubic centimeters greater than that of blood plasma. Five minutes after intravenous injection of 20 per cent solution of glucose at a rate of 0.5 gram of glucose per kilogram of body weight, the sugar content of lymph from the liver was approximately 50 milligrams per 100 cubic centimeters higher than that of lymph from the thoracic duct. When the rate of flow of lymph from the two sources is considered, this finding would appear to indicate that glucose was more diffusible through the capillary bed of the liver than through that of the remaining part of the body drained by the thoracic duct.

Study of the effect of feeding was made on 5 dogs with a lymphatic fistula of the liver and on 18 with a fistula of the thoracic duct. The rate of flow of lymph, which was increased in

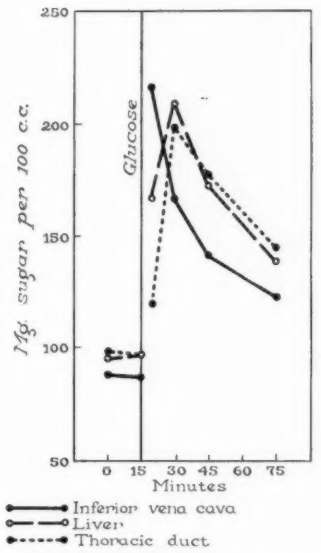

Fig. 2. Effect of intravenous injection of 0.5 gram of glucose per kilogram of body weight on the sugar content of hepatic lymph, of lymph from the thoracic duct and of blood plasma.

all instances after feeding, reached a peak during the second hour and remained greater than the rate before feeding for at least 5 hours. The type of meal fed was not important. The rate of flow of lymph from the liver was increased approximately 108 per cent and that from the thoracic duct approximately 79 per cent over normal. The difference between these two percentages is probably not of great significance.

The effect of brief exercise on flow of lymph was studied. The dogs were allowed to walk on the level at a rate of 40 yards per minute, and the rate of flow of lymph was noted at intervals of 5 and 10 minutes. These studies were made on 5 dogs with a lymphatic fistula of the liver and on 8 dogs with a fistula of the thoracic duct. The increase in the rate of flow of lymph from the liver was approximately 83 per cent and that from the thoracic duct was approximately 270 per cent over normal. This result would be expected because of the effects of muscular movement and of massage in the region of the large lymphatic bed drained by the thoracic duct.

The chloride content of hepatic lymph and that of lymph from the thoracic duct were essentially the same and were consistently 10 to 40 milligrams per 100 cubic centimeters greater than that of blood plasma.

The values for inorganic phosphate in the lymph from the liver and thoracic duct and in blood plasma were approximately the same, but the value for alkaline phosphatase in the lymph from both the liver and the thoracic duct was consistently 30 to 50 per cent less than the value for that in blood plasma.

Studies were made to determine the effect of acute and chronic poisoning with carbon tetrachloride on the flow of lymph. Two dogs were permitted to breathe, for 1 hour, a mixture of carbon tetrachloride and air; the mixture, which consisted of 1 cubic centimeter of carbon tetrachloride per 10 liters of air, was circulated at a rate of 10 liters per minute. There was slight, if any, increase in the rate of flow of lymph from either the thoracic duct or the lymphatic vessel of the liver after this exposure. The lymph from the liver in all instances was distinctly bloody.

The lymphatic vessel of the liver was cannulated in 2 dogs with cirrhosis that had been produced with treatments of carbon tetrachloride 3 times a week for 5 months. The lymphatic vessels of the liver were dilated to an extreme degree, and the rate of flow was increased approximately 10 to 20 times normal. A fistula of the thoracic duct was made in 1 dog in which cirrhosis of 9 months' duration had been produced by administration of carbon tetrachloride. In this dog the rate of flow of lymph was only 2 to 3 times normal. In all dogs with chronic carbon tetrachloride poisoning, definite evidence of jaundice, ascites, and cirrhosis appeared. The content of bilirubin in lymph was approximately the same as that in blood plasma.

Ligation of the common bile duct resulted in an immediate rise in the content of bilirubin in hepatic lymph. In 2 dogs with fistulas of both the thoracic duct and the lymphatic vessel of the liver, the occurrence of an immediate rise in the content of bilirubin in hepatic lymph, with no rise of that in lymph from the thoracic duct, was additional evidence that all the hepatic lymph was being collected.

SUMMARY

The average rate of flow of hepatic lymph was 2.26 cubic centimeters per 10 minutes as compared with 4.6 cubic centimeters per 10 minutes for that of lymph in the thoracic duct. Probably hepatic lymph contributed a fourth to a half the total volume of lymph in the thoracic duct.

Intravenous administration of 20 per cent solution of glucose as a lymphagogue was followed by an increase of approximately 70 per cent in the rate of flow of lymph from both the liver and the thoracic duct.

Ingestion of food and brief periods of exercise were followed, in each instance, by an increase in the rate of flow of lymph from the thoracic duct and the liver. Ingestion of food increased the rate of flow of lymph from the thoracic ducts by approximately 80 per cent and that of hepatic lymph by approximately 105 per cent. Exercise increased the rate of flow in the thoracic duct much more precipitously than that from the hepatic fistula, probably because of the massaging effect of exercise on the large lymphatic beds.

Acute poisoning with carbon tetrachloride caused no gross change in the flow of lymph, but hepatic lymph became bloody. In the presence of cirrhosis caused by exposure to carbon tetrachloride the rate of flow of hepatic lymph was greatly increased but that of lymph from the thoracic duct was only moderately increased.

The protein content of hepatic lymph was approximately five-sixths that of blood plasma and that of lymph from the thoracic duct was approximately half that of blood plasma. Lymph from both the liver and thoracic duct contained sugar and chloride slightly in excess of that found in blood plasma, the content of inorganic phosphate was the same in all 3 and the value for alkaline phosphatase was 30 to 50 per cent lower in lymph from each source than in blood plasma.

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GELATIN NEPHROSIS

Renal Tissue Changes in Man Resulting from the Intravenous Administration of Gelatin

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THE currently increased interest in and greater use of gelatin as a blood substitute in the treatment of peripheral vascular collapse and as a means of parenteral nutrition demands a careful evaluation of any pathological changes for which this substance may be responsible. Three years ago the appearance of striking tubular hydropic degeneration, similar to that seen in sucrose nephrosis (1, 2, 14) but now occurring in the kidneys of patients who had not been subject to sucrose therapy, directed our attention to the possible etiologic rôle of gelatin in the production of these lesions. Recently Popper and associates published a report on the use of gelatin in the treatment of shock, and, noting similar renal tubular swelling in some of their necropsy cases, also suggested that these lesions might be attributable to intravenous gelatin therapy. Continued association with a surgical service on which extensive studies of the use of gelatin intravenously have been carried out (4–7) and on which major surgical procedures are a common occurrence has presented an unusual opportunity for the further study of this lesion. The present study was accordingly undertaken in order to evaluate the rôle of gelatin in the pathogenesis of the lesion, to study the morphological nature of the changes which were produced, and to appraise their functional significance.

MATERIALS AND METHODS

The study is based on the postmortem examinations of 23 patients who received gelatin intravenously in quantities ranging from 100 to 17,600 cubic centimeters with widely varying intervals between the final injection and the death of the patient. The gelatin, derived from pig skin, was given in an 8 per cent solution in physiological saline, usually in doses of 800 cubic centimeters (4).

All the patients, save 2, had neoplastic growths primary in the tissues of the abdominal cavity. Of the exceptions, one suffered with a squamous cell carcinoma of the lower lip and the other from a chronic bleeding gastric ulcer. All but 3 died of their primary disease and its complications or from complications resulting from the surgical procedures, most of which involved extensive regional resections. In most instances the gelatin therapy was given in association with the surgical procedures and either instituted as part of the preoperative preparation or, more commonly, begun at and continued for varying intervals following the operation.

The postmortem examinations were all performed within 17½ hours of death; in the majority of instances the postmortem interval was 2 to 10 hours. Blocks of renal tissue were fixed in Zenker's solution at the time of necropsy, embedded in celloidin and sectioned at 8 microns. The tissues were stained with Heidenhain's iron hematoxylin, Heidenhain's modification of Mallory's phosphotungstic acid hematoxylin, and Delafield's hematoxylineosin stain. In 1 case, No. 6507, alcohol fixed tissues were stained with Best's carmine for glycogen.

PATHOLOGICAL RENAL CHANGES

Grossly, kidneys with well developed gelatin nephrosis are swollen and the cut surfaces tend to bulge. The average weight of 17 otherwise relatively normal kidneys from 10 patients (excluding the kidneys of these patients which showed any neoplastic infiltration) in this series who demonstrated well developed microscopic lesions was 210 grams.

Microscopically the lesions are similar to those described for sucrose nephrosis (Fig. 1)

From the Department of Pathology, The University of Chicago.

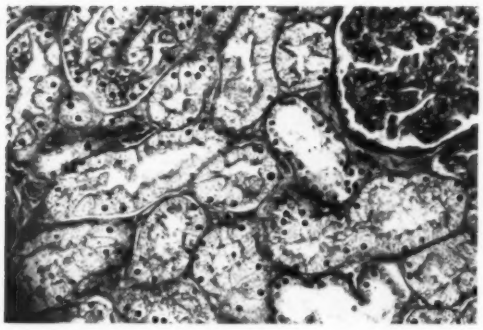

Fig. 1. Case 6558. The general pattern of the renal lesion in sucrose nephrosis. The patient received 80 cubic centimeters of 50 per cent sucrose solution intravenously 29 hours before death. There is marked vacuolization of the convoluted renal tubules. Compare with Figure 3. Heidenhain's modification of Mallory's connective tissue stain. ×160.

(1, 2, 14). Variations in the extent and the degree of change can be roughly correlated with the time elapsing between the injection of the gelatin solution and the examination of the kidney, and with the amount of gelatin given (Table I). The epithelial cells of the proximal convoluted tubules present a granular, finely vacuolated swelling, often so severe that the tubular lumens are evident only as slits (Fig. 2). Occasionally the affected cells are necrotic but this change is minimal and the cells are, on the whole, well preserved. In fresh, well fixed tissues the brush border remains distinct and is not sloughed. These changes are largely confined to the proximal convoluted tubules and the portions of these tubules which lie in the medullary rays and extend into the renal medulla show the earliest and most pronounced swelling and vacuolization. The distal convoluted tubules may also be affected, though to a lesser degree, but the loops of Henle and the collecting tubules remain free from this change even in the severest gelatin nephrosis encountered (Figs. 3 and 4). Best's carmine stain on the alcohol fixed kidney sections of Case 6507 gave no evidence of glycogen in the hydropic tubular cells.

The lumens of the convoluted tubules and of the glomerular spaces contain much amorphous granular precipitate. This may be indicative of dysfunction, tissue necrosis, or of the presence of gelatin in the tubular lumens, but its significance is obscured by the fact that such precipitates are routinely encountered in the tubules of otherwise normal kidneys examined at necropsy.

No significant glomerular changes have been noted which are not attributable to other renal changes. Changes such as the leucocyte infiltration and shrinkage of glomerular tufts described by Anderson and Berthea (2) for sucrose nephrosis have not been seen. One case (Case 6412, Fig. 5), having well developed gelatin nephrosis together with a complicating icteric nephrosis, displayed a striking cuboidal epithelial metaplasia of the parietal layer of Bowman's capsule adjacent to the neck of the convoluted tubules. This change is morphologically similar to that which has been described by Anderson and Berthea for sucrose nephrosis and to that which has been described by Bywaters and Dible as occurring in association with the renal lesion of the crush syndrome.

In a number of instances large amounts of gelatin were administered over long periods of time, the greatest amount being 17,600 cubic centimeters administered in 23 doses over a period of 34 days. One case only (Case 6305, Fig. 6) showed moderate focal colloidal droplet degeneration of the tubular epithelium. In other instances where varying amounts of gelatin were given but discontinued sufficiently long before death to allow the hydropic swelling to subside (Table I) no changes definitely attributable to the previously existing gelatin nephrosis were demonstrable. The changes seen were such as are routinely encountered in relatively normal kidneys of patients dying with high fever or other generalized disturbances. Only occasional tubules were necrotic, displaying pyknotic nuclei and isolated foci of regenerating tubular cells.

FACTORS INFLUENCING THE DEVELOPMENT OF GELATIN NEPHROSIS

Table I summarizes the major findings pertaining to the degree of gelatin nephrosis, the extent of gelatin therapy, other hypertonic intravenous fluids given, and the basic pathological condition of the patient as well as any renal change other than the gelatin nephrosis.

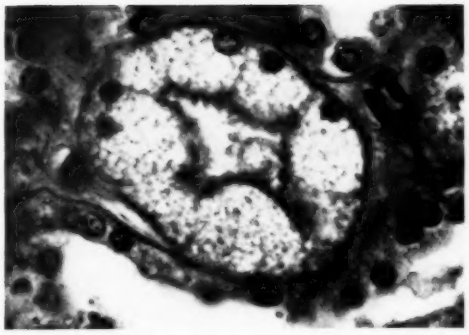

Fig. 2. Case 6206. There is marked hydropic swelling of the illustrated proximal convoluted tubule. The brush border is intact. On the whole the cells are well preserved. Heidenhain's modification of Mallory's connective tissue stain. ×655.

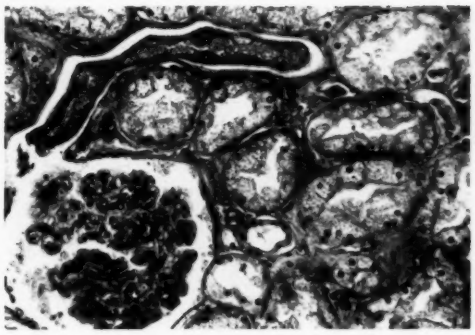

Fig. 3. Case 6206. The general pattern of the lesion of gelatin nephrosis in the renal cortex. The proximal convoluted tubules display marked vacuolization; the loops of Henle remain free from such change. Heidenhain's modification of Mallory's connective tissue stain. ×160.

It reports all instances of patients receiving gelatin which were encountered in this study.

The most important single factor determining whether or not gelatin nephrosis was present was the time interval between gelatin administration and death. All cases examined within 67 hours of receiving their last gelatin injection showed gelatin nephrosis. No patient expiring more than 120 hours after receiving the last gelatin injection displayed the change. In this connection it is interesting to recall the recent work of Little and Dameron indicating that in dogs given gelatin intravenously only traces of gelatin can be found in the urine after 72 hours. The shortest interval between gelatin administration and death was seen in Case 6317 where the elapsed time was given as 5 minutes in the nursing notes. Though there is basis for questioning the exactness of this figure it is certain that the gelatin was given less than 30 minutes before death. The lesions in this instance were well developed but present only focally in portions of the proximal convoluted tubules lying in the medulla (Fig. 7). The spotty distribution of these lesions is in harmony with recent studies indicating that the individual nephrons each function only part of the time. Their appearance so shortly after the injection of gelatin agrees well with the observation of Little and Dameron that in dogs 50 per cent of the gelatin injected intravenously disappeared from the plasma within 30 minutes. By the third postinjection hour the proximal convoluted tubules exhibited well developed and widespread lesions. These convoluted tubules then persisted as long as gelatin was administered.

Inspection of Table I reveals that some correlation is possible between the severity of the lesion and the amount of gelatin given in that the severest lesions (4 plus) tend to be present in the instances where the greatest amount of gelatin was given. This correlation is not absolute (see Case 6206), factors of length of postinjection interval and individual variability tending to obscure the picture.

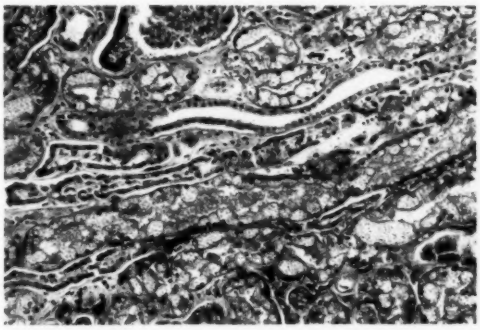

Fig. 4. Case 6206. The general pattern of the lesion in the cortex and medullary rays in gelatin nephrosis. The proximal convoluted tubules show marked vacuolization and many are filled with granular débris. The longitudinal section of a loop of Henle illustrated shows no vacuolization. Heidenhain's modification of Mallory's connective tissue stain. ×100.

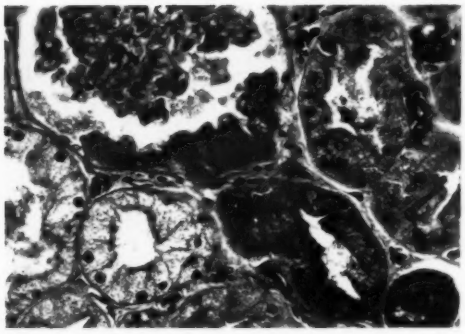

Fig. 5. Case 6412. Cuboidal metaplasia of the parietal cells of Bowman's capsule. The kidneys showed combined gelatin and icteric nephrosis. Heidenhain's modification of Mallory's connective tissue stain. ×220.

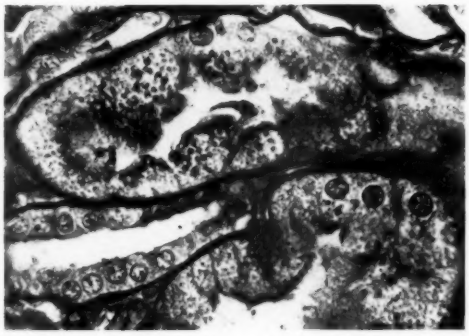

Fig. 6. Case 6305. Colloid droplet degeneration of proximal convoluted tubules; 10,630 cubic centimeters gelatin given intravenously in 13 injections in 16 days. Heidenhain's modification Mallory's connective tissue stain. ×460.

Rigdon and Cardwell suggested that the state of hydration of the patient is of importance in determining the occurrence of sucrose nephrosis. The material available did not permit an evaluation of this factor in the pathogenesis of gelatin nephrosis. This series is also not sufficiently extensive to permit judgment as to whether or not previous renal disease will enhance the lesion.

EFFECT OF GELATIN NEPHROSIS ON RENAL FUNCTION

No consistent, accurate measure of renal function was made on these patients clinically since they did not evince clinical renal dysfunction. The occasional pertinent blood and urine studies recorded gave no substantial evidence of impaired renal function. A careful study of the fluid balance of the patients was made from the clinical records. These studies were frequently complicated by the fact that in most instances the gelatin therapy was begun at the time of operation. Concomitantly increased fluid administration and fluid and blood loss through inadequately measured emesis and drainage and from surgical loss of blood often obscured possible changes such as the early diuresis noted by Bridger and associates in dogs receiving intravenous gelatin.

Case 6532 (Fig. 8) demonstrated the most striking change which might possibly be attributed to gelatin therapy. A marked diuresis occurred 12 days after laparotomy, on the third and last day of gelatin administration. This persisted for 6 days and then subsided. The only other intravenous fluid administered during this time was 5 per cent glucose solution and no other medication was given which might be held accountable for the diuresis. Comparable quantities of glucose were given daily from the third postoperative day (14 days before the diuresis developed) through the twenty-second postoperative day (the day the diuresis subsided). A second patient (Case 6542) had a satisfactory urine output of 1000 cubic centimeters on the second postoperative day. On the third day he was given a first injection of 400 cubic centimeters of gelatin solution intravenously. His urine output on this day dropped to 50 cubic centimeters despite a total of 4900 cubic centimeters of intravenous fluid given. On the 2 succeeding days he received a total of 6,650 cubic centimeters of fluid intravenously, including 400 cubic centimeters of gelatin, but put out only 100 cubic centimeters of urine per day and expired on the sixth postoperative day without having established adequate urine output. The day before his death blood chemistry studies showed serum chloride 108.5 millimoles per liter, serum *p*H 7.32, serum carbon dioxide 18.5 millimoles per liter and blood nonprotein nitrogen of 117.6 milligrams per cent. The only significant lesion in the kidneys at necropsy was gelatin nephrosis. A complicating factor in the interpretation of these findings was the myocardial infarction

TABLE I.—SUMMARY OF THE SEVERITY OF GELATIN NEPHROSIS, THE AMOUNT OF GELATIN THERAPY GIVEN, OTHER INTRAVENOUS THERAPY EMPLOYED, AND THE BASIC PATHOLOGICAL CONDITION OF THE PATIENTS STUDIED.

Case No.	Gelatin nephrosis	Interval between last gelatin and death	Total c.c. gelatin given	No. of doses	Total days of gelatin therapy	Other i.v. hypertonic fluids[1]	Remarks[2]
			Gelatin Given—Gelatin Nephrosis Present				
6317	+	5 min.	100	1	1	50% glucose	Resected left hypernephroma. Acute dilatation of the stomach. Death: 3rd day.
6257	+++	3 hr.	400	1	1	Amigen	Resected esophageal carcinoma. Death: 11th day.
6172	+++	3 hr.	5,200	6	10	50% glucose	Resected ovarian carcinoma. Peritonitis. Arteriolonephrosclerosis. Death: 10th day.
6206	++++	8 hr.	1,600	2	2	Amigen	Carcinoma of the lip. Coronary thrombosis.
6301	++	16 hr.	800	2	4	Amigen	Resected esophageal carcinoma. Death: 4th day.
6725	+++	16 hr.	1,600	3	2	none	Resected esophageal carcinoma. Hemorrhage from duodenal ulcer. Death: 35th day.
6507	+++	16 hr.	2,300	3	3	Amigen	Resected gastric carcinoma. Death: 4th day.
6445	+++	16 hr.	2,400	3	5	none	Resected carcinoma of cervix uteri. Colostomy repair. Fecal peritonitis. Death: 4th day.
6420	++	24 hr.	11,200	14	16	none	Resected gastric carcinoma. Fecal peritonitis. Death: 20th day.
6485	++++	24 hr.	11,600	15	20	none	Linitis plastica. Jejunostomy. Pulmonary embolism. Death: 17th day.
6498	+	30 hr.	400	1	1	Amigen	Resected esophageal carcinoma. Death: 2nd day.
6305	++++	33 hr.	10,630	13	16	Amigen	Gastric carcinoma with carcinomatosis. Peritonitis. Death: 12th day.
6220	++++	48 hr.	12,000	15	24	none	Resected retroperitoneal lymphosarcoma. Renal metastases. Death: 19th day.
6412	+++	50 hr.	800	1	1	Amigen	Resected carcinoma of gall bladder. Peritonitis. Icteric nephrosis. Death: 17th day.
6542	+++	67 hr.	800	2	2	50% glucose	Resected rectal carcinoma. Myocardial infarction. Death: 7th day.
6524	+++	119 hr.	800	1	1	50% glucose	Resected gastric ulcer. Peritonitis. Death: 5th day.
6337	++	23 days	8,535	12	29	Amigen	Lymphoblastic sarcoma. Extensive abdominal resection. Right hydronephrosis. Death: 54th day.
			Gelatin Given—No Gelatin Nephrosis				
6201	....	86 hr.	800	1	1	none	Resected rectal carcinoma. Death: 4th day.
6233	....	90 hr.	7,600	10	15	50% glucose Amigen	Resected duodenal carcinoma. Bronchopneumonia. Death: 8th day.
6402	....	19 days	17,620	23	34	none	Resected carcinoma of colon. Bronchopneumonia. Death: 52nd day.
6191	....	45 days	6,665	18	27	none	Resected gastric carcinoma with metastases and emaciation. Death: 71st day.
6386	....	102 days	800	1	1	Amigen	Resected pancreatic carcinoma with metastases and emaciation. Death: 102 days.
6532	....	147 days	2,400	3	3	none	Resected mammary carcinoma. Abdominal carcinomatosis. Death: 158th day.

[1]Includes only fluids given within the last 7 days preceding death. [2]Day of death given is the postoperative day.

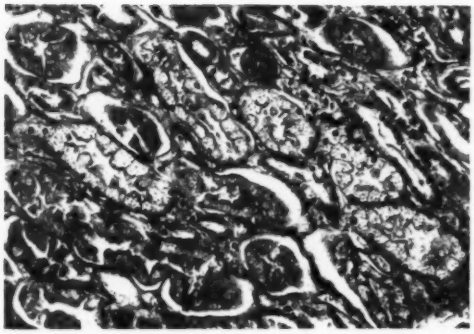

Fig. 7. Case 6317. Early focal gelatin nephrosis. There is well developed vacuolization of the convoluted tubules. The patient received 100 cubic centimeters of gelatin intravenously within half an hour of his death. Heidenhain's modification of Mallory's connective tissue stain. ×160.

developing on the third postoperative day. His blood pressure subsequently remained at about 86/60 to 100/80 (preoperative pressure, 145/80) till the day of death.

DISCUSSION

Three of the cases presented raise the question of another possible effect of gelatin injection. Case 6206 had suffered from several attacks of "indigestion" during the past few years. On April 5, 1944, at 2:30 p.m. he was given 800 cubic centimeters of gelatin intravenously. Throughout the following day he had vague abdominal distress and mild substernal pain, felt nauseated, and noted excessive sweating. At 2:45 p.m. of this day intravenous injection of 800 cubic centimeters of gelatin solution was begun. After receiving about 200 cubic centimeters he complained of severe substernal pain, became cyanotic and his breathing became shallow. Two hours later he complained of severe epigastric pain boring to the back, his blood pressure was unobtainable and at 10:35 p.m. he expired with extensive myocardial infarction demonstrated at necropsy. Another patient (Case 6542) was found cold and sweating on the morning of his third postoperative day. His blood pressure was 70/60. Saline, blood, amigen, and 400 cubic centimeters of gelatin solution were given intravenously. Seventeen and a half hours later he was given an additional 400 cubic centimeters of gelatin and 1000 cubic centimeters of amigen; 67 hours later he expired with extensive myocardial infarction. Both patients had severe coronary arteriosclerosis. The third (Case 6485) developed thrombosis of left iliac vein and artery postoperatively while receiving gelatin and other fluids intravenously and died of pulmonary embolism 24 hours after the last gelatin injection.

Intravenous injection of gelatin is known to produce circulatory changes. Fletcher and associates as well as Holt and Knoefel demonstrated an increase in blood volume greater than the volume of gelatin injected, this apparently being due to the effect of gelatin in drawing additional fluid into the circulation. The former investigators did not note any excessive strain on the cardiovascular systems of their patients or volunteer subjects though they did note a marked increase in cardiac output and a sustained hemodilution. They urged caution in the use of gelatin and other macromolecular substances in chronically ill patients. Hanzlik and Karsner demonstrated pseudoagglutination of erythrocytes in the form of conglutinated thrombi in postmortem sections of a guinea pig receiving 0.5 per cent gelatin intravenously. Ivy and associates noted similar marked pseudoagglutination and an increase in the sedimentation rate in dogs given 5 per cent gelatin solution intravenously. Similar observations on patients have been reported by Kozoll and associates (19, 25). Earlier reports (24) indicated that gelatin given intravenously increases the viscosity and coagulability of the blood. Subcutaneous injections of gelatin have been used in the past to increase the coagulability of the blood in the treatment of aneurysms. Recently Koop and associates following an extensive investigation, reported that the clotting time after gelatin infusion is uniformly prolonged in dogs but was unaffected in 6 of 7 patients studied. The seventh patient demonstrated an appreciably prolonged clotting time. Steigmann and associates found no pathological changes in bleeding time, clotting time, or platelet counts of patients given gelatin infusion and Gordon and associates found no postmortem evidence of thrombosis, hemolysis, embolism, or capillary damage in dogs given 8 to 10 per cent solutions of gelatin intravenously.

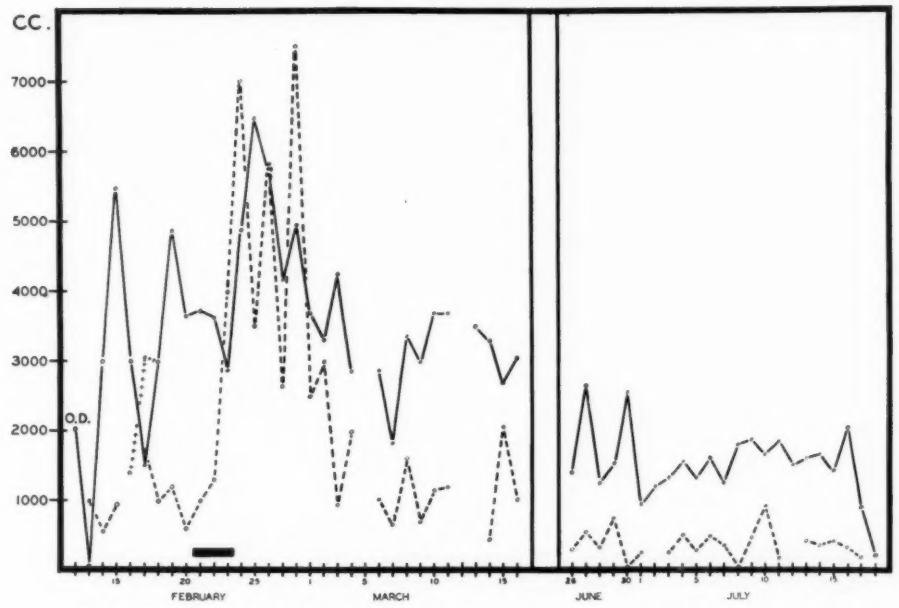

Fig. 8. Case 6532-L.B. Fluid balance record. Total intake, o———o; total output, o+++o; urine output, o– – –o; gelatin given, ———.

In the light of these reports, conflicting though the conclusions sometimes are, the 3 cases reported above, though not conclusively implicating gelatin, suggest the need for caution against the indiscriminate use of gelatin intravenously administered to patients with circulatory disturbances and vascular disease. It may be that some of the conflicting reports may be due to the variability of gelatin preparations. A report by the National Research Council indicates that at least some of the local thrombotic effects reported may be due to added preservatives.

This series of necropsy studies would seem clearly to establish the etiological rôle of gelatin in the production of hydropic swelling of renal tubules. Well developed lesions were found in all postmortem examinations of kidneys of patients receiving gelatin intravenously within 67 hours of the time of death. Heuper found similar lesions in dogs given gelatin solution intravenously. Similar well developed lesions were not found in over 400 consecutive cases studied except in those instances in which sucrose therapy had been employed. Minimal lesions were occasionally encountered which corresponded to the minimal lesions seen in some of the patients who had received gelatin so long before death that the residual changes could only be attributed to gelatin by inference. The etiology of these changes was not clearly demonstrated but the changes were such as might be attributed to other intravenous fluids.

The effect of other intravenous fluids was evaluated. Cutler reported finding hydropic changes in the kidneys of patients receiving hypertonic solutions of dextrose (10-15 per cent solutions). Nearly all the patients in our series received dextrose intravenously, some receiving relatively large amounts of 10 per cent solution over long periods. This may in some instances have enhanced the effect of the gelatin but other patients receiving similar amounts of dextrose without concomitant gelatin showed only minimal or equivocal tubular vacuolization. Five of these patients received 50 per cent dextrose intravenously,

usually in 1 or 2 doses of 50 cubic centimeters each during the week preceding their demise. No tubular lesions were found. One patient (Case 6233) received 250 cubic centimeters of 50 per cent dextrose during the 48 hours before death but displayed no renal lesion at necropsy. Amigen was frequently administered together with gelatin. A number of control cases receiving amigen without concomitant gelatin failed to demonstrate nephrotic renal changes.

The pathogenesis of gelatin nephrosis is not demonstrated by this study. Wilmer in discussing the mechanism of sucrose damage to the kidneys concluded that this effect was osmotic, the sucrose diffusing into the renal tubular cells and drawing in water. He noted that rats and rabbits phloridzinized to prevent sucrose reabsorption still developed hydropic changes of the renal tubules. It is probable, as also suggested by Popper and associates that gelatin nephrosis develops in much the same manner, the gelatin arriving in the tubular cells by diffusion or active absorption, or both, and causing in turn the taking up of water by increased osmotic pressure exerted by the gelatin. The ready reversibility of the change in both cases speaks in favor of this concept.

Though no uniform, clearly demonstrable harmful effects have as yet been attributed to gelatin nephrosis, it is well to bear in mind the growing feeling that the morphologically similar sucrose lesion is not innocuous. Feher and associates reported that in dogs having an initial large renal reserve, no demonstrable effect on the blood nonprotein nitrogen was found when sucrose was injected though the ability of the kidneys to concentrate urine was reduced. In dogs with relative renal excretory insufficiency, produced by Goldblatt's method of producing hypertension or by temporarily occluding the renal arteries for 1 hour, marked reduction in the ability to concentrate urine and a transient rise in blood nonprotein nitrogen occurred when sucrose was injected intravenously. A report by the National Research Council points out that it is not known whether the use of gelatin will impair functional return to normal in kidneys in sustained ischemia or severe burns or in the crush syndrome. Anderson and Berthea (2) recommend that sucrose be withheld from patients with renal lesions and state that it should in no instance be given in large or repeated doses. The 2 cases reported as showing diuresis and oliguria in the presence of gelatin injection, warrant a similar caution in the use of gelatin.

SUMMARY

1. The postmortem findings of 23 patients receiving intravenous gelatin therapy, who expired as a result of medical and neoplastic disease or from complications of therapeutic surgical measures, are reported as demonstrating the etiologic rôle of gelatin in the pathogenesis of renal hydropic changes morphologically similar to those produced by the intravenous injection of sucrose.

2. The morphology of the renal lesion produced by gelatin is described and compared with that of surcrose nephrosis.

3. Gelatin nephrosis is shown to be a reversible change occurring within half an hour after the intravenous injection of gelatin and disappearing within 120 hours following the last injection.

4. Studies of the effect of the renal lesion on renal function are reported as inconclusive but 2 suggestive cases are discussed, one showing diuresis and the other oliguria following the intravenous administration of gelatin. Caution is suggested in the use of this substance in patients exhibiting previous renal impairment.

5. Attention is directed to the possible rôle of gelatin in promoting circulatory disturbances and 3 cases are reported as suggesting gelatin as a potential precipitating factor in coronary occlusion and vascular thrombosis in the presence of circulatory disturbances and vascular disease.

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SODIUM PENTOTHAL ANESTHESIA FOR SELECTED VAGINAL OBSTETRICS

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THE use of intravenous sodium pentothal in obstetrics is not new, several reports having appeared in the literature during the past 10 years (3, 5, 8, 9, 12, 14). Some have employed it as the sole or major anesthetic agent routinely or almost routinely in obstetrics (3, 8, 12), whereas LaBrecque reserved it for use in cases with severe upper respiratory infection, bronchitis, asthma, tuberculosis, bronchiectasis, and after ingestion of large meals. Hunt and Lundy employ it in connection with local infiltration for cesarean section, withholding the use of pentothal until the abdomen has been entered and the operator is ready to proceed with incision of the uterus and immediate extraction of the fetus. Several (8, 9) contend that it is an unsatisfactory anesthetic agent for podalic version with extraction on the grounds that the relaxation which it produces is inadequate. Hellman (3) and Rucker (13) do not agree with this contention in view of the fact that 1.5 per cent of Hellman's operative deliveries and 7.3 per cent of Rucker's deliveries involving a viable infant were effected by this method.

Our use of intravenous sodium pentothal anesthesia for vaginal delivery was instituted during World War II because of the shortage of anesthetists available for routine ward deliveries. It had been immediately preceded by essentially routine use of perineal block anesthesia. Originally, open drip ether was given by various untrained hospital employees, but this was abandoned after the occurrence of a serious case of vomiting under ether anesthesia followed by aspiration pneumonia which necessitated hospitalization of the patient for almost 3 months. That older members of the staff could not recall other similar tragic or near-tragic cases is truly remarkable.

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In order to complement local anesthesia, we scanned the field for an anesthetic agent with reasonable safety, whose technique of administration could be mastered with little extra instruction, whose contraindications were few, and which might be administered to private patients in view of the fact that relatively very few of our private physicians ever used local anesthesia even though adequate equipment for its use was immediately available. One of us (A. L. D.) had employed intravenous sodium pentothal anesthesia routinely for minor and for selected major gynecological operations for a number of years and had observed its routine use for vaginal obstetrical deliveries. The choice of this drug as an anesthetic agent for selected vaginal obstetrical deliveries has proved most gratifying to both house staff and private physicians although some of the latter early employed it with misgivings.

Sodium pentothal is a barbiturate which differs little in chemical structure from pentobarbital sodium (nembutal), sodium amytal, and evipal soluble, being most like nembutal. Induction of anesthesia is incredibly short and quiet, the patient generally being unconscious within 20 to 30 seconds and ready for surgery within 1 minute after the first few cubic centimeters of solution have been administered into the vein. Vomiting during or after its administration is rare. Recovery is rapid though the patient may remain drowsy for 1 to 3 hours after anesthetization, depending in large measure upon the amount of premedication. There is seldom any hang over. Pentothal is rapidly destroyed in the body, probably by the liver although Lundy (10) has suspected it in the urine. It does not have any effect upon the blood chemistry except for a practically negligible elevation of blood sugar. The blood picture is unaltered and metabolism unaffected. It produces a moderate respiratory

depression with anesthetic dosage, but this is not alarming. Pentothal will effect an elevation of blood pressure, particularly systolic, but the elevation is not sustained though the immediate systolic rise may amount to as much as 20 millimeters of mercury (8). It leaves the pulse unaffected or somewhat slower. Other pharmacological characteristics have no clinical bearing. Laryngospasm is frequently mentioned as an effect of intravenous sodium pentothal anesthesia but actually appears to be rather uncommon, more particularly when its use is preceded by a hypodermic of atropine or of hyoscine.

Intravenous sodium pentothal rapidly traverses the uteroplacental barrier to depress fetal respiratory movements and to retard the initiation of respirations in the newborn. Hellman, Shettles, and Stran (4) found that within 10 or 12 minutes it reaches equal concentrations in fetal and maternal blood. They found that during the first 5 minutes after beginning the anesthetic, little of the drug reached the fetus. Dreisbach and Snyder showed that when the experimental rabbit was given 10 milligrams of pentothal intravenously per kilogram of body weight at term, the fetal respiratory rate was decreased to one-third the initial rate for a period of about 5 minutes, and that after a total dose of 3 to 5½ times the above amount there was relatively little cumulative effect upon the fetus. In this connection it should be pointed out that the above smallest experimental dose is comparable to the average total dose used in our series.

It has been suggested that intravenous sodium pentothal should be avoided as an anesthetic in certain toxemia patients because of the presumed destruction of the drug by the liver and the possibility of added degenerative changes in that organ (11). The frequent moderate elevation in systolic blood pressure might also be used as an argument against its use in connection with the severe hypertensive toxemias of pregnancy. However, Rucker (13) seems not to have considered this maternal complication as a serious contraindication to its use. In general, however, there seem to be few valid contraindications to its use in obstetrics. It is conceded that pentothal with its respiratory depressant effect is undesirable in heart disease with decompensation, with marked anemia, in the face of dyspnea attributable to pathological processes in the thorax, or if there is any reason to think that the respiratory passage is, or may become, obstructed. It is ideal that the stomach should be empty in order to eliminate vomiting. Also, pentothal is known to increase laryngeal reflexes and vomiting would then tend to increase the incidence of laryngospasm. There are individual idiosyncrasies to pentothal, but these are surely uncommon. Hunter has reported a case with cutaneous manifestations in the form of erythema multiforme followed by pustule formation and pyrexia when the anesthetic was later repeated. It goes without saying that the solution should be injected intravenously and not into the extravenous tissues nor into the arterial tree. Lundy (10) records several cases of intra-arterial injection of sodium pentothal. All of these patients experienced varying amounts of pain in the injected arms. One of these succumbed to an overdose of pentothal. The induction of anesthesia in this case was prolonged with an excessive amount administered. Death followed the delayed entrance of the overdose of the drug into the general vascular system via the arterial as compared with the intravenous route. Lundy advises the use of an intermittent tourniquet to the affected arm and oxygen inhalation whenever a large amount of the drug is administered intra-arterially. Dixon and Lundy (10) have indicated that 10 per cent concentrations of sodium pentothal injected into the perivenous or subcutaneous tissues produce pain and irritative manifestations, sometimes even with sloughing of tissue, but Jarman claims that 5 per cent solutions are almost innocuous when injected into these tissues and that it is unusual for these patients to complain of even a sore arm. Lundy (10) says that thrombosis was frequent with 10 per cent solutions but that its incidence has been reduced in proportion to the reduction in concentration of the drug.

Between July 24, 1945, and October 1, 1946, 350 patients from both ward and private services of the Hermann Hospital were delivered of viable pregnancies under intravenous so-

dium pentothal anesthesia. Ward patients selected for this type of anesthesia were those in whom there was every reason to believe that delivery of the child could be completed promptly after induction of anesthesia, i.e., before the usual time required for an appreciable amount of the barbiturate to reach the fetal circulation. Few premature deliveries involving living fetuses were effected under this anesthetic for the service policy is to conduct premature labors without analgesia and with delivery under local infiltration anesthesia in order to avoid all respiratory depressant drugs. Moreover, it is the departmental rule that approximately one-half of all ward cases must, for purposes of house staff training, be delivered under perineal block anesthesia. Aside from these exceptions, there was no conscious selection of patients from the ward service. Within a very short period of time, many of the private patients were also being delivered under this anesthetic.

The material used was provided in a two ampule carton. One ampule contained 1 gram of sodium pentothal powder and the other 50 cubic centimeters of sterile distilled water from which the 2 per cent solution was freshly prepared for each patient. The special sets kept handy for this use contained two 20 cubic centimeter syringes, rubber tubing with adaptor for syringe and needles, and 3 needles —1 No. 18 and 2 smaller needles. A metal syringe holder was clamped to the side of the delivery table and the patient's arm fixed to an armboard. The patient was prepared in lithotomy and draped for delivery. The bladder was generally catheterized during the process of induction of anesthesia. The accoucheur designated when he was ready to proceed with the actual delivery. An antecubital vein was usually selected for puncture and the vein catheterized in order to reduce the possibility of extravenous injection. Two or 3 cubic centimeters of the 2 per cent solution were injected initially. The patient was then asked to count out loud and an additional 2 to 3 cubic centimeters injected every 20 to 30 seconds until the patient ceased to count, after which an additional 5 cubic centimeters were given. By this time, the patient was generally ready for vaginal examination or delivery. At the slightest movement on the part of the patient, an additional 5 cubic centimeters of the drug was injected. An airway was used only when anesthesia was quite deep. If apnea appeared, the injection was stopped until respirations began again. A wisp of cotton or tab of tissue paper suspended over the nostrils was soon abandoned for there was never any difficulty in determining that respirations existed. The level of anesthesia was generally not deep and respiratory efforts were moderately full. Also, oxygen administered until after delivery was abandoned as unnecessary for such brief periods of anesthesia.

For spontaneous delivery, this procedure was only slightly modified. With the onset of the uterine contraction selected for final delivery, induction of anesthesia was begun. The patient was encouraged to bear down with the pains until the fetal head began to crown and the accoucheur was able to reach the fetal chin. Then, as soon as obstetrical anesthesia could be obtained, he would proceed with spontaneous delivery aided by the Ritgen maneuver or possibly assisted by mild suprafundic pressure. No great amount of fundic pressure was ever employed and none except with a uterine contraction. Delivery and episiotomy were otherwise performed as with any other anesthetic. The umbilical cord was clamped promptly after delivery in order to make certain that the flow of pentothal from mother to child ceased.

The great majority of these anesthetics were given by members of the department of obstetrics. The departmental affiliation and rank of the anesthetist in each case is shown in Table I. Those rotating internes on the obstetrical service desirous of learning the technique of intravenous sodium pentothal anesthesia were allowed to give a limited number of these anesthetics under strict supervision of an obstetrical resident and near the end of their time on the service. Generally speaking, their preliminary knowledge of obstetrics was to their advantage and they accounted for fewer anesthetic difficulties than did house officers without previous obstetrical experience. Two obstetrical residents accounted for 47 per cent of all anesthetics or 50 per cent of those given by their department.

TABLE I.—ANALYSIS OF 350 PATIENTS DELIVERED UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO DEPARTMENTAL AFFILIATION AND RANK OF ANESTHETIST

Department		No. patients	Per cent
Obstetrical staff		330	94.3
Resident	236		
Interne	93		
Visiting	1		
Anesthesia staff		20	5.7
Resident or interne	19		
Professional anesthetist	1		
Totals		350	100.0

Race and economic level, the latter determined from admission status, of each patient in the series will be seen in Table II. The hospital has no accommodations for private colored obstetric patients. The distribution between the races for both ward and private patients is roughly the same as for these services as a whole. Sixteen private physicians delivered patients under intravenous sodium pentothal anesthesia but 9 of these can be considered casually for each accounted for a maximum of only 3 deliveries. This does not mean that the 9 tried and discarded pentothal for short vaginal delivery but that their number of deliveries over the period of time under consideration was correspondingly low. Thirty was the maximum number of deliveries accounted for by any one private physician.

Age of patient is recorded in Table III. Since there was no selection of patients for pentothal anesthesia on the basis of age, the observed age distribution is essentially the same as for the service as a whole. Two patients were less than 15 years old; actually, each was 14 when delivered.

Mention has already been made of the departmental policy of preferring no analgesia

TABLE II.—RACE AND ECONOMIC LEVEL OF 350 PATIENTS DELIVERED UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA

Race and economic level	No. patients	Per cent
Ward colored	128	
Ward Mexican	44	62.3
Ward white	46	
Private white	130	37.7
Private Mexican	2	
Totals	350	100.0

TABLE III.—AGE DISTRIBUTION OF 350 PATIENTS DELIVERED UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA

Age, years	No. patients	Per cent
15 or less	4	1.1
16–19	69	19.7
20–24	125	35.7
25–29	76	21.7
30–34	42	12.0
35–39	30	8.6
40–43	4	1.1
Totals	350	99.9

and local infiltration anesthesia for the handling of premature labor and delivery. There were, however 7 premature births in this series. Two of these involved intrapartum fetal death due to premature separation of the normally implanted placenta, each at 30 weeks' gestation. The remaining 5 premature deliveries advanced to 34 weeks' (1 case) and 35 weeks' (4 cases) gestation were effected with dispatch so that the premature infants with birth weights ranging from 4 pounds 6 ounces to 5 pounds 3½ ounces were born without narcosis, required no resuscitation and were all raised. The remaining 343 (98%) gestations produced near-term, term, and postmature fetuses, i.e., each newborn was at least technically of term size—weighed at least 2500 grams (5½ pounds).

Table V reveals that there was no selection of patients in regard to previous obstetrical experience. Fifty-three per cent were multiparas, only 4 being in the grande multipara range. One of the essential primiparas had had 6 previous abortions, 2 had had 2 each, and 14 had each previously aborted once. There were 4 young primiparas, i.e., patients delivering a term or near-term pregnancy before the sixteenth birthday anniversary. They

TABLE IV.—ANALYSIS OF 350 PATIENTS DELIVERED UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO DURATION OF GESTATION

Weeks' gestation	No. patients	Per cent	
30–32	2	0.6	
34–35	5	1.4	
36–37	51	14.6	
38–39	106	30.3	98
40–41	152	43.4	
42–44	34	9.7	
Totals	350	100.0	

TABLE V.—ANALYSIS OF 350 PATIENTS DELIVERED UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO PARITY

Parity	No. patients	Per cent
Primigravidas	147	42.0
Essential primiparas	17	4.9
Multiparas	186	53.1
1 previous viable birth — 108		
2 previous viable births— 47		
3 previous viable births— 14		
4 previous viable births— 8		
5 previous viable births— 5		
7 previous viable births— 1		
8 previous viable births— 2		
9 previous viable births— 1		
Totals	350	100.0

were all ward patients, 1 being a Mexican 15 years old and 3 colored, one 15 years, and two 14 years of age. Four patients were true elderly primiparas, i.e., were delivered of the first viable pregnancy after the thirty-fifth birthday anniversary. One of these was a 39 year old private white woman and the others colored patients 36 to 39 years of age. Five were elderly essential primiparas or were delivered of the first term or near-term pregnancy after age 35, but in each instance the viable pregnancy had been preceded by 1 or more abortions. Four of these were white private patients each of whom had had 1 previous abortion; the oldest was 42 years of age; 1 colored elderly essential primipara was 37 years old and had had 2 previous abortions.

The various primary fetal presentations and positions are recorded in Table VI. Manual

TABLE VI.—ANALYSIS OF 350 PATIENTS DELIVERED UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO PRIMARY FETAL PRESENTATION AND POSITION

Presentation or position	No. patients	Per cent of total	
L. O. A.	158 (a)	44.9	
L. O. T.	21	6.0	
L. O. P.	24	6.8	95.7
R. O. A.	75 (a)(b)	21.3	
R. O. T.	16	4.5	
R. O. P.	43	12.2	
Breech	11		3.1
Face	2		0.6
Transverse	1		0.3
Compound	1 (b)		0.3
Totals	352		100.0

(a) Twin pregnancy. (b) Represents 1 fetus.

or forceps rotation from an occiput transverse or posterior to an anterior was employed 35 times.

In Table VII it will be seen that 110 fetuses (31.3%) were delivered spontaneously under intravenous sodium pentothal anesthesia. This figure is almost identical to that reported by Eastman (3), whereas Rucker (13) reports only 8.3 per cent spontaneous deliveries when a viable infant was involved. LaBrecque reports the highest incidence of spontaneous delivery, namely 57 of 80 deliveries (71%), with the use of either sodium pentothal or evipal soluble. In this connection it must not be forgotten that pentothal will efface bearing down efforts in 60 per cent of the patients anesthetized with it, whereas evipal does not unfavorably affect this reflex mechanism (9). The low incidence of podalic version and of midforceps delivery in the current series reflects the conservatism of the service. The version and extraction was performed on the patient with transverse presentation of the fetus and prolapse of the umbilical cord. One midforceps delivery was used for delivery of a second twin while the other 2 midforceps deliveries occurred on the private service. Perineorraphy for correction of a previously noted

TABLE VII.—ANALYSIS OF 350 PATIENTS DELIVERED UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO METHOD OF DELIVERY OF FETUS AND FATE OF THE PERINEUM

Method of delivery		No. patients	Per cent
Spontaneous delivery		110	31.3
With episiotomy	54		
With 1° perineal tear	11		
With 2° perineal tear	5		
Without perineal tear	40		
Low forceps delivery		226	64.4
With episiotomy	205 (a)		
With 1° perineal tear	4		
With 2° perineal tear	4		
With 3° perineal tear	1		
Without perineal tear	12		
Breech extraction		11	3.1
With episiotomy	9		
With 1° perineal tear	1		
Without perineal tear	1		
Podalic version, extraction without tear		1	0.3
Midforceps delivery with episiotomy		3 (a)	0.9
Totals		351	100.0

(a) Includes one of a set of twins.

TABLE VIII.—ANALYSIS OF 350 PATIENT DELIVERIES UNDER SODIUM PENTOTHAL ANESTHESIA ACCORDING TO RANK OF ACCOUCHEUR

Rank of accoucheur		No. patients	Per cent
Rotating interne		130	37.1
Resident obstetrician		87	24.9
For private physician	1		
With aid of staff physician	2		
Private obstetrician		133	38.0
Private patients	131		
Ward cases	2		
Totals		350	100.0

rectocele was performed in connection with 8 private deliveries. One vaginal and 2 cervical tears were known to have occurred with low forceps delivery and all were repaired under pentothal anesthesia. Forceps to the aftercoming head were applied in 5 instances, Mauriceau maneuver being employed in the other 6 breech deliveries.

The accoucheur for each delivery is recorded in Table VIII. Only 2 ward deliveries were not actually effected by the house staff—the version with extraction and a difficult low forceps due to an excessive-sized fetus with erythroblastosis associated with a contracted pelvis.

As previously stated, a 2 per cent solution of pentothal was administered intravenously. The amounts of the drug employed are shown in Table IX. Unfortunately, the amount used was not recorded in 100 (28.6%) of the cases. Of the remaining 250 in which the exact amount administered is known, only 21 (8.4%) received more than 50 cubic centimeters (1.0 gm.). The largest amount given, 135 cubic centimeters (2.7 gms.), was for the Mexican woman with a contracted pelvis and an excessive-sized erythroblastotic, stillborn (intrapartum death) delivered by prolonged and difficult low forceps extraction. She had received little analgesia. Spontaneous delivery without perineal repair was effected once with only 6 cubic centimeters of solution and a breech extraction of a stillborn premature (intrapartum death) without repair in another instance with 8 cubic centimeters. The average for the series was 39 cubic centimeters (0.78 gm.). In large measure, the amount of anesthesia varied with the amount and recency of administration of analgesia, but such correlations cannot be graphically shown by usual methods. However, the various analgesic drugs with time interval between last dosage and moment of birth of the child are recorded in Table X. Of interest are the great variety of drugs and combinations of these used to obtain analgesia. It was rather surprising to discover that 182 patients, 58.7 per cent of those receiving analgesia, received the last dose of the analgesic less than 2 hours before delivery of the infant. Obviously, this fact must be remembered when noting the

TABLE IX.—ANALYSIS OF 350 DELIVERIES UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO AMOUNT OF DRUG EMPLOYED IN 2 PER CENT SOLUTION

Amount, cubic centimeters	No.	Per cent of total	Per cent of recorded	
10 or less	4	1.1	1.6	
11 to 20	33	9.4	13.2	
21 to 30	36	10.3	14.4	91.6
31 to 40	77	22.0	30.8	
41 to 50	79	22.6	31.6	
51 to 60	5	1.4	2.0	
61 to 70	6	1.7	2.4	
71 to 80	6	1.7	2.4	8.4
81 to 90	1	0.3	0.4	
91 to 100	2	0.6	0.8	
Above 100	1	0.3	0.4	
Not recorded	100	28.6		
Totals	350	100.0	100.0	

TABLE X.—ANALYSIS OF 350 DELIVERIES UNDER SODIUM PENTOTHAL ANESTHESIA ACCORDING TO ANALGESIC DRUGS GIVEN AND TIME INTERVAL BETWEEN LAST ANALGESIC DOSE AND BIRTH OF INFANT

Analgesic drugs administered	No. patients	Per cent	Time from last dose to delivery	
			Range mins.	Average mins.
Demerol and hyoscine	161	46.0	10 to 465	120
Demerol alone	80	22.9	10 to 2400	150
Demerol with seconal, nembutal, or luminal	24	6.9	30 to 1050	198
Pantopon or dilaudid with seconal or nembutal	20	5.7	30 to 2190	235
Phenobarb. or luminal	6	1.7	20 to 1060	280
Seconal or nembutal	15	4.3	30 to 465	205
Hyoscine with seconal or nembutal	2	0.6	30 to 75	53
Codeine or morphine	2	0.6	240 to 440	340
None	40	11.4		
Totals	350	100.0		

TABLE XI.—ANALYSIS OF 14 DELIVERIES UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO SUPPLEMENTARY ANESTHESIA EMPLOYED

Perineal block for episiotomy repair		3
Following use of 1 gm. i.v. pentothal		4
Perineal block	2	
Open ether	1	
Nitrous-oxide	1	
For partial spontaneous breech delivery		2
Perineal block	1	
Nitrous-ether	1	
Ether until arrival of anesthetist		1
Nitrous adjuvant experiment		1
Ether after extravenous pentothal		1
Vomiting under pentothal		2
Finished with perineal block	1	
Finished with cyclopropane	1	

dosage of anesthesia required. It must also be remembered as a factor in the production of apnea in the newborn infant.

As will be seen in Table XI, 14 patients (4.0%) received supplementary anesthesia. In addition to these, perineal block was the original anesthetic agent which was abandoned for intravenous sodium pentothal when the patient was declared "too unco-operative" (2 cases), when an unfavorable fetal position was discovered at vaginal examination (2 cases), and when 1 delivery was unduly prolonged due to fetopelvic disproportion. Actually, the supplementary anesthesia given was rarely the result of failure of pentothal anesthesia. For example, one accoucheur was so suspicious of pentothal that he effected delivery (3 cases) under it but completed perineal repair under local infiltration. In 4 cases supplementary anesthesia was used in order to avoid preparation of a second gram of pentothal solution. In another instance, the resident experimented with nitrous oxide as an adjuvant to pentothal. In the final analysis, then, intravenous sodium pentothal was seriously or majorly complicated in only 3 instances, an incidence of 0.86 per cent. In the first of these, the drug itself cannot be blamed, for it was administered into the tissues outside the venous system. Moreover, in the other 2, there is reason to suspect that better control of the sodium pentothal anesthetic or of vaginal manipulation might have avoided complications, for in one the patient is said to have been "hard to manage under pentothal," in other words, delivery was effected or at least attempted without obstetrical anesthesia, while the other vomited after delivery of the child, a time when the original dose frequently wears off. The latter patient swallowed so much air that Wangensteen suction had to be employed 8 hours later.

The case of the patient receiving extravenous injection of sodium pentothal warrants more detailed presentation. She was a 26 year old secundipara with a normal pregnancy at term who was given demerol (100 mgm.) and hyoscine (gr. 1/150) both intravenously 2½ hours before delivery and demerol (100 mg.) subcutaneously 1 hour before delivery. Anesthesia was attempted with the usual 2 per cent solution of sodium pentothal. After the injection of 30 cubic centimeters with no apparent anesthetic response from the patient, open drip ether was substituted. The intravenous needle had apparently perforated both vein walls with the pentothal injected beneath a fascial plane since blood had initially been drawn back into the syringe and there was no tumefaction in the subcutaneous area. After an episiotomy had been done and the child delivered by low forceps extraction, it was noted that the patient's respirations were mildly depressed. The child was in good condition. The episiotomy was repaired without further administration of an anesthetic. The mother's respiratory depression was apparently from absorption of pentothal but was combatted with coramine. She slept for 3 hours after delivery. Some 14 hours later, the patient complained of pain in the right arm and several areas of hyperemia were noted near the site of venipuncture. There was little swelling in this area and the corresponding ulnar pulse was normal. Hot moist applications to the affected area were continued for 3 days when the arm became comfortable and there was apparently no residual effect from this accident. As previously noted, cases of this kind followed by irritative symptoms, even sloughing of tissue, are known to occur with 10 per cent solutions but not with concentrations of pentothal not in excess of 5 per cent.

Complications of pregnancy, labor, and the puerperium are listed in Tables XII, XIII, and XIV, respectively. It will be noted that

TABLE XII.—ANALYSIS OF 350 DELIVERIES UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO COMPLICATIONS OF PREGNANCY

Complication		No. patients	Per cent
Contracted pelvis		50	14.3
G. C. F.	6		
Funnel typical	18		
G. C. T.	23		
G. C. R.	2		
Simple flat	1		
Toxemia		63	18.0
Pre-eclampsia, mild	27		
Pre-eclampsia, severe	34		
Arteriolosclerosis	1		
Arteriolosclerosis with superadded pre-eclampsia	1		
Anemia, due to iron deficiency		10	2.9
Ascaris infection (with anemia)		1	0.3
Heart disease (class II)		2	0.6
Prolonged pregnancy		1	0.3
Syphilis		11	3.1
Primary	1		
Latent, Wassermann pos.	7		
Latent, Wassermann neg.	3		
Myomata uteri		4	1.1
Rectal stricture		1	0.3
Cystocele and/or rectocele		6	1.7
Hemorrhoids		2	0.6
Condylomata accuminata		1	0.3
Multiple, twin (double ovum)		1	0.3
Adenoma of breast		1	0.3
None		196	56.0
Totals		350	100.1

TABLE XIII.—ANALYSIS OF 350 DELIVERIES UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO COMPLICATIONS OF LABOR

Complication		No. patients	Per cent
Premature rupture of membranes, spontaneous		40	11.4
Intrapartum fever		4	1.1
Induction of labor		18	5.1
Medical	7		
Membrane rupture	11		
Precipitate labor		16	4.6
Prolonged labor		10	2.9
Eclampsia		1	0.3
Pneumonia		1	0.3
Premature separation placenta		2	0.6
Prolapse of umbilical cord		1	0.3
Excessive-sized fetus		13	3.7
Low implantation of placenta		1	0.3
Adherent placenta (manual removal)		5	1.4
Hematoma of vagina		1	0.3
Third degree perineal laceration		1	0.3
Cord around fetal neck		62	17.7
Once	51		
Twice	8		
Thrice	3		
True knot in cord		2	0.6
None		172	49.1
Totals		350	100.0

TABLE XIV.—ANALYSIS OF 350 DELIVERIES UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO COMPLICATIONS OF PUERPERIUM

Complication		No. patients	Per cent
Puerperal morbidity		39	11.1
Puerperal infection	27		
Pyelitis	8		
Mastitis (?)	3		
Scarlet fever	1		
Sterilization		10	2.9
Hemorrhage		4	1.1
Premature separation placenta	2		
With uterovag. pack	1		
With pack of vagina	1		
None		297	84.9
Totals		350	100.0

56 per cent of the patients had no complication of pregnancy, 49 per cent had none in labor, and 85 per cent none in the puerperium. Moreover, 105 patients, or 30 per cent, had normal pregnancies, labors, and puerperia.

Intravenous sodium pentothal anesthesia, as noted previously, does not affect uterine contractility or contractions. The average estimated blood loss in this series of deliveries was 168.4 cubic centimeters and the distribution of estimated blood loss is recorded in Table XV. In order to ascertain whether estimated blood loss varied with anesthetics other than pentothal, 100 consecutive cases were reviewed of patients delivered in the same period of time, under other anesthetics but by the same group of accoucheurs who had used intravenous sodium pentothal anesthesia. No statistical difference could be found in any anesthetic group nor in any group of accoucheurs—rotating internes, residents, or private physicians. Local, caudal, spinal, saddle block, and various inhalation anesthetics and combinations thereof, except chloroform, were included in this differential study. It seems safe to say, therefore, that intravenous sodium pentothal anesthesia does not increase blood loss in the placental stage. Neither does it appear to decrease the amount of bleeding in that stage.

It is not easy to evaluate the amount of resuscitation required by a group of newborn infants delivered by a heterogenous group of physicians and house officers since some employ oxygen, vitamin K, coramine, or even a

TABLE XV.—ANALYSIS OF 350 DELIVERIES UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO ESTIMATED AMOUNT OF BLOOD LOSS

Estimated blood loss, cubic centimeters	No. patients	Per cent	
0 to 100	116	33.1	
125 to 200	165	47.1	
225 to 300	49	14.0	
350 to 400	12	3.4	
600	1	0.3	1.2
800	3	0.9	
Not estimated	4	1.1	
Totals	350	99.9	

TABLE XVI.—ANALYSIS OF 351 NEWBORN INFANTS FROM 350 DELIVERIES UNDER INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA ACCORDING TO AMOUNT OF RESUSCITATION REQUIRED IN EACH

Resuscitation required		No. patients	Per cent
No resuscitation required		270(a)	76.9
Slight or little resuscitation required		44	12.5
Narcosis	9		
Loop of cord about neck	2		
Cyanosis	1		
Aspirated amniotic fluid	2		
Cause unknown	30		
Moderate resuscitation required		21	6.0
Analgesia	7		
Premature complicated delivery	1		
Cyanosis, cause unknown	1		
Analgesia, cord about neck	4		
Premature, intrapartum infection	1		
Erythroblastosis	1(b)		
Traumatizing delivery	1		
Pre-eclampsia	1		
Pentothal 16 mins., midforceps	1		
Unknown cause	3		
Considerable or much resuscitation required		12	3.4
Analgesia	3		
Asphyxia, unknown cause	2		
Analgesia, premature	1		
Analgesia, fetal distress	1(c)		
Cord about neck, fetal distress	2(d)		
Long labor, pre-eclampsia	1		
Traumatizing delivery	2(e)(f)		
Intrapartum death—stillborn, nonmacerated		3	0.9
Premature separation placenta	2		
Prolapse cord—transverse presentation	1		
Antenatal death—stillborn, macerated		1	0.3
Erythroblastosis	1		
Totals		351	100.0

(a) One found dead in crib, believed suffocated at age 6 hours.
(b) Lived 12 hours.
(c) Demerol-hyoscine 70 minutes before delivery, cord around neck, passed much meconium stained amniotic fluid, lived 3½ hours.
(d) One of these received no analgesia, admitted directly to delivery room, had aspirated much meconium stained mucus, lived 6 hours.
(e) Breech broken up, contracted pelvis, forceps to aftercoming head, leg broken, lived 5 hours.
(f) Difficult breech extraction, excessive size fetus (10 lbs. 10 ozs.), lived 9 hours, autopsy cerebral hemorrhage.

mechanical resuscitator if the newborn child does not cry vigorously and promptly after delivery. However, it was found, as shown in Table XVI, that 270 or 77 per cent of these newborns required no resuscitation whatsoever, i.e., cried or at least breathed regularly and promptly after delivery. Forty-four or 12.5 per cent required little or only slight resuscitation. In these, aspiration of mucus or amniotic fluid was followed by mild cutaneous stimulation in the form of rubbing the back or thumping the toes or fingers. Pure oxygen was administered to 9 of these, but in each instance it is stated that resuscitation was of minor importance. That pentothal was responsible for apnea in these is far from proved. Actually in one the drug could not have played a rôle, for the child was born before the patient could be completely anesthetized. However, in 9 instances the newborn is said to have been mildly narcotized, in 2 there was a loop of umbilical cord about the fetal neck, in 1 mild cyanosis, in 2 much aspirated amniotic fluid, and in the remaining 30 there was no recorded or recognizable reason for the mild initial apnea. Analgesic drugs appear to be involved especially in the light of their frequent administration late in labor. However, all the above 314 newborns (89.5%) requiring little or no resuscitation were actually born alive in good condition and survived the immediate neonatal period with a single exception—1 requiring no resuscitation, found dead in its crib 6 hours after delivery, believed to have suffocated, in which autopsy revealed only adrenal hemorrhage.

There remain 37 infants, 10.5 per cent of the series, in which minor degrees of resuscitation were inadequate. All but 1 of the infant deaths are included in this group. The apparent causes for major degrees of resuscitation or of fetal loss are included in Table XVI. In no case did sodium pentothal *per se* appear to play any serious rôle in resuscitation or in survival of the newborn. The most serious effect of pentothal in this series was noted in a second twin delivered by midforceps extrac-

tion whose mother had been anesthetized for 16 minutes before this co-twin was born. The newborn was obviously narcotized and required moderate resuscitation but survived and was apparently undamaged. One could hardly expect ill effects upon the newborn with delivery planned to be completed within 8 minutes of induction of pentothal anesthesia. The records are not adequate enough to show the time interval between induction of anesthesia and delivery of the child, but it is believed that 8 minutes was rarely exceeded and most often not nearly approached.

In the series, there were 10 infant deaths for an uncorrected total fetal mortality rate of 2.86 per cent. The infant mortality rates at Hermann Hospital for 1945 and 1946, during which years the sodium pentothal series was obtained, are compared in Table XVII with figures from the current series. Since there was a certain amount of selection in the pentothal series, the infant mortality rates are not exactly comparable to the rates for the individual calendar years.

Of the 10 infant deaths in this series, 4 were stillborn. Only 1 was macerated, antenatal death occurring in a prolonged pregnancy with an excessive-sized erythroblastotic fetus while the remaining 3 intrapartum deaths were due to premature separation of the normally implanted placenta (2 cases), and to prolapse of the umbilical cord associated with transverse presentation of the fetus.

One of the 6 neonatal deaths has already been mentioned in connection with resuscitation, the child being born alive in apparently good condition, requiring no resuscitation, and 6 hours later being found dead in its crib, presumably due to suffocation. In 1 instance, the patient was admitted directly to the delivery room, and immediately delivered, without analgesia, by low forceps extraction. The umbilical cord was once around the fetal neck, the fetus had aspirated meconium and survived 6 hours. Another was delivered by easy low forceps extraction with poor application of the forceps. Demerol and hyoscine had been given 70 minutes before delivery, much meconium had been passed in the terminal part of the first stage of labor, the umbilical cord was once around the fetal neck, and the child lived only 3½ hours. It appears that in these 2 cases the loop of cord about the fetal neck was responsible for fetal distress, yet in 4 other instances its presence was associated with moderate resuscitation, in 2 with the necessity for little resuscitation, whereas in 54 more such instances the child required no resuscitation and was born alive in good condition. One child with serious erythroblastosis fetalis succumbed 12 hours after delivery. The remaining 2 neonatal deaths are attributable to traumatizing delivery by breech extraction. One weighed 10 pounds 10 ounces, required a long and difficult extraction, lived 9 hours, and at autopsy showed cerebral hemorrhage. The final case was one of breech position, in which the breech was decomposed with difficulty and extracted. This child lived only 5 hours and autopsy showed atelectasis and confirmed the fracture of one leg. There is no reason to assume that pentothal anesthesia was in any way the cause of any of these infant deaths.

TABLE XVII.—INFANT MORTALITY RATES IN 350 CASES DELIVERED BY INTRAVENOUS SODIUM PENTOTHAL ANESTHESIA COMPARED WITH THE HOSPITAL'S RATES FOR 1945 AND 1946

	Year 1945 per cent	Year 1946 per cent	Current series per cent
Total gross fetal mortality	4.66	4.56	2.86
Total stillborn mortality	2.56	2.12	1.14
Total neonatal mortality	2.10	2.44	1.71

There were no maternal deaths.

In conclusion, we are not claiming any outstanding advantages for intravenous sodium pentothal anesthesia even in selected vaginal deliveries and are neither using nor recommending it as a routine obstetrical anesthetic. However, in our hands it admirably solved an embarrassing anesthetic situation. As used in a small series and in 2 per cent solution, we have found it safe for mother and child. Its margin of safety seems to be such that a careful obstetric resident can quickly master the technique of its administration and can give it with little risk to patients. As such, it appears to be ideally adaptable to emergency obstetrical use but perhaps not to the casual

anesthetist. We are continuing to employ it in this manner and are convinced that it has a definite and permanent place in obstetrical anesthesia.

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ANDROLOGIC ENDOCRINOLOGY

Correlation of Clinical Symptoms, Urinary Hormone Excretion and Testicular Cytology

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THE diagnosis and classification of testicular failure (13) requires consideration of the dual function of the testis from the standpoint of etiology, pathology, hormonology, and clinical symptoms. Several groups of workers have correlated recently these features of patients with intrinsic testicular disease.

Heller, Nelson, and Roth (6) employed the term "functional prepuberal castrates" to describe patients with agenesis, hypoplasia or preadolescent atrophy of the testes and with wolffian duct remnants (epididymis and vas deferens). The testes of these patients are completely lacking in both functional seminiferous and androgenic tissue. Accordingly there is azoospermia and failure of development of the sexual characteristics (change of voice, appearance of body and genital hair, and growth and maturation of the genitalia). The urinary excretion of 17 ketosteroids and estrogens is low or low normal and the urinary excretion of gonadotropins is characteristically increased, due to compensatory pituitary hyperactivity. Although delayed epiphyseal closure may result in eunuchoid proportions, these patients are of normal or short stature.

Klinefelter and associates have described another group of patients with partial testicular hypoplasia or atrophy. The subsequent studies of Heller and Nelson (5) have defined the clinical, pathologic, and hormonal characteristics of the entire syndrome. There is total destruction of the seminiferous apparatus with partial or no damage of the androgenic elements. Azoospermia is invariably present. Androgenic function may be normal or severely deficient. The urinary excretion of 17 ketosteroids and estrogens ranges from normal to very low levels and that of the gonadotropins always shows compensatory elevation. A significant number of these patients has gynecomastia. The habitus ranges from eunuchoid to normal. This group of workers has presented a concordance of clinical symptomatology, testicular histology, hormone excretion and present concepts of hormonal interrelations of the testis.

The 8 patients reported by us illustrate some of the remaining discrepancies in current concepts of testicular function and pathology.

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METHOD OF SELECTION AND STUDY OF PATIENTS

The workup of each patient included a complete history and physical examination, routine blood and urine studies, determination of the basal metabolism, roentgenograms of the sella turcica and of long bones for osseous age determination, special blood chemistry as indicated, testicular biopsy, and urinary hormonal studies. The testicular tissue obtained at biopsy was fixed immediately in Bouin's fluid, embedded in paraffin, sectioned, and stained with hematoxylin-eosin and with Masson and Mallory stains; reticulum stains were done when indicated. Urinary hormonal studies were based on a minimum of 4 to 6 consecutive 24 hour specimens. There were isolated 17 ketosteroids by extraction with carbon tetrachloride (7) and by purification with Girard reagent; values were determined photoelectrically by the color reaction with m-dinitrobenzene (8, 16); the results are expressed as milligrams per 24 hours. In patient 8, the Oesting method for 17 ketosteroids was used. Gonadotropins were determined by a modification of the method of Heller and

Chandler (4), devised by Salmon in our laboratory. The method involves dialysis and alcohol precipitation of refrigerated 24 hour specimens, dehydration, extraction, and bioassay employing immature female rats; the results are expressed as rat uterine units, rat ovarian units, and gross corpora lutea units per 24 hours.

PROTOCOLS OF PATIENTS

Patient 1. This 34 year old farmer entered the hospital because of bilateral inguinal hernias and varicose veins.

The clinical history revealed that he had been "always" nervous and subject to palpitations, and that he experienced muscular cramps in the arms and legs. He had passed, a year previously, a renal calculus. There was nocturia of three to four times and occasionaliy enuresis. Maturation had been rather slow; the ages at which his voice changed and pubic hair appeared were not recalled, but he shaved for the first time at the age of 20 years.

The physical characteristics are shown in Figure 1a. The blood pressure was 110/76 millimeters of mercury. The skin had a dry, inelastic, almost senile appearance. There was no pectoral hair; the axillary and pubic hair was normal in amount and in distribution; the facial hair was confined to the upper lip and to the chin, and it was very sparse. In the left lobe of the thyroid, there was a 3 centimeter, firm nodule which subsequently was shown to be a fetal adenoma. There were bilateral inguinal hernias and varicosities of the legs. The penis measured 3.8 inches in length and 3.5 inches in circumference at the corona. The scrotum was somewhat underdeveloped. The testes measured 1.5 by 0.75 inches and were fairly soft. The prostate was of normal size and consistency. The height was 74 inches, the span 72.5 inches, and the ratio of the upper half to the lower half of the body was 35 to 39. The weight was 127 pounds.

Routine laboratory studies revealed normal blood and urine. The basal metabolic rate was −25 per cent. Roentgenograms of the chest and sella turcica were normal.

Examination of the seminal specimen, which was 1 cubic centimeter in volume, showed no spermatozoa.

Urinary hormone data included a 17 ketosteroid excretion of 6.6 milligrams per 24 hours (normal 11 to 20 mgm. per 24 hours) and a gonadotropin excretion of 25 rat uterine units, 12 rat ovarian units, 4 rat corpora lutea units per 24 hours (normal values 6 to 10, 3 to 7, 0 to 2 units per 24 hours, respectively).

Histological studies of the biopsied testes showed that the normal architecture was grossly distorted by the loss of many seminiferous tubules as well as by a great hyperplasia of the Leydig cells (Fig. 2a). Some of the better preserved tubules showed a single layer of spermatogenic cells enclosed by a dense, hazy, hyalinized basement membrane which had a fibrillar structure or resembled closely Askanazy's degeneration seen in tuberculous meningoarteritis (Fig. 2b). Twisted columns of dense hyaline material represented the end stages of tubular deterioration. In some areas there was an increase in the number of blood vessels and some of the arteries appeared unusually thick walled. The remainder of the tissue showed a diffuse or nodular hyperplasia of the Leydig cells. In some areas the Leydig cells were greatly hypertrophied. Often they were arranged in cords or sheets and in these areas there was fair uniformity of appearance; the cell size was relatively normal and the cytoplasm thready and deep-staining, with a peripheral pale or almost foamy zone (Fig. 2b). The cell boundaries appeared very indistinct. In other areas small groups of cells were supported by a delicate fibrillar stroma; these cells usually showed a foamy cytoplasm. In still other areas groups of very small Leydig cells with proportionately small but vesicular nuclei were found; the cytoplasm of these cells stained very densely. There were occasional regions in which the size of the cells showed remarkable variation even in a small field. Some of the nuclei were gigantic and rather irregular in outline with a dense, granular chromatin network. The nucleoli were very prominent. Golden pigment was found in the cytoplasm of some cells, but no crystalloids were present.

In summary, the clinical evidence of hypoandrogenism was manifested by the eunuchoid build, the scanty body hair and very sparse beard, the senile skin, and the small testes. The nervousness, muscular cramps and urinary frequency possibly may have been symptoms of androgenic failure. Azoospermia was present. The hormonal studies showed a 17 ketosteroid output of less than half the normal value whereas the urinary excretion of gonadotropin was approximately twice the maximum normal level. Despite these findings (highly suggestive of Leydig cell failure), the testes showed massive Leydig cell hyperplasia; moreover, large numbers of these cells appeared entirely normal when studied by available histological methods.

Patient 2. This 18 year old millworker entered the hospital because of a slipped femoral epiphysis.

The clinical history revealed that he was the tallest member of his family and that he had always been thin. His voice changed at 14 years of age and pubic hair appeared at 17 years. No axillary hair had appeared and he had not shaved. He claimed normal heterosexual interests but had not had sexual intercourse. His height was 58 inches at 15 years of age and 70 inches at 18 years; he subsequently grew 4 inches in the following year and one-half.

The physical characteristics are shown in Figure 1b. The blood pressure was 105/75 millimeters of mercury. There was poor muscular development and the joints were loose and hyperextensible. A slipped femoral epiphysis was demonstrated. There was no facial or axillary hair and the pubic hair was very scanty. The penis measured 6 inches in length and 5 inches in circumference at the corona. The scrotum was well developed. The testes measured approximately 1.0 by 0.75 by 0.75 inches. The prostate was normal in size and in consistency. The height was 74 inches; the span was 74 inches; and the ratio of the upper half to the lower half of the body was 32 to 42. The weight was 114.5 pounds.

Routine laboratory studies revealed normal blood and urine. The serum cholesterol was 173 milligrams per cent. The basal metabolic rate was −4 per cent. Visual fields were normal. A roentgenogram of the chest was normal. Roentgenograms of the skull showed a bridged sella turcica, absence of the frontal sinus and very few mastoid air cells. The osseous age was +10 to −14 years at the chronological age of 18, and was +14 to −16 years at the age of 19.5.

Examination of the seminal specimen, 0.5 cubic centimeter in volume, showed no spermatozoa.

The urinary hormone data included a 17 ketosteroid excretion of 11.3 milligrams per 24 hours and a gonadotropin excretion of 25 rat uterine units, 20 rat ovarian units, and less than 10 corpora lutea units per 24 hours.

Histological studies of the biopsied testes showed that the general architecture of the tissue was well preserved (Fig. 2c). The tubules were of normal size. The basement membrane was normal in the majority but in a few tubules it showed slight thickening and hyalinization. Within the tubules there was only a single layer of cells among which Sertoli cells were conspicuous (Fig. 2d). No unequivocal spermatogonia or spermatid stages were found. In some areas and usually near the periphery of the biopsy specimen, the tubules were slightly distended by basophilic concretions which were granular or concentrically ringed, and contained occasional minute particles of highly refractile material. These masses compressed the tubular lining to a single layer of flat cells with dark, almost pycnotic nuclei and in advanced stages of the lesion caused disintegration of the tubular wall. The stroma was of delicate, fibrillar character. The Leydig cells were ample in number and were scattered diffusely throughout the stroma in groups of 3 to 10 cells. The majority was of normal size, but occasionally hypertrophied cells collected in groups which attained the size of a tubule. A fair proportion of the Leydig cells had a milky or foamy cytoplasm, but there were many cells which had an almost homogeneous, indistinct, weakly acidophilic cytoplasm (Fig. 2d). The nuclei were of normal size, oval in contour and showed the usual diffuse chromatin network. The nucleoli often were unusually prominent. No pigment or crystalloids were seen and no vascular changes were observed.

In summary, the clinical evidence of hypoandrogenism of this patient consisted of eunuchoid build, retarded development of scanty pubic hair, absence of beard or body hair, poor muscular development, small testes (with a large penis), and delayed ossification of the long bones. Azoospermia was present. The 17 ketosteroid value of 11.3 milligrams per 24 hours just fell within the lower limits of normal and the gonadotropin output was twice the maximum normal level (practically identical with patient 1). Despite this 17 ketosteroid level which was almost double that of patient 1, there were actually far fewer Leydig cells present, and these occurred in small groups and strands rather than in the hyperplastic masses seen in the first patient.

Patient 3. This 17 year old student entered the hospital for the investigation of small testicles.

The clinical history revealed that pubic hair appeared at approximately 12 to 13 years of age. He shaved at the age of 17 years and he has shaved once or twice per week since that time. His physical strength always had been poor. The sexual outlook and activity were said to be normal.

The physical examination showed a definitely feminine habitus and the patient appeared somewhat younger than his age. The voice was adolescent in character and it continued so for several years. The beard and body hair were very sparse; there was moderate axillary hair, and scanty pubic hair of feminine distribution. The nipples were prominent and erectile. The hips were wide. The penis was about three-fourths of normal size. The scrotum was well formed and the testes were one-half normal size and were soft in consistency. The prostate was approximately one-half inch in diameter. The height was 69.5 inches; the span was 71.5 inches; and the ratio of the upper half to the lower half of the body was 35 to 34.5. The weight was 135 pounds.

Routine laboratory studies revealed normal blood and urine. Basal metabolic rate ranged from −12 to −23 per cent. The visual fields were normal. Roentgenogram of the sella turcica was normal. The epiphyses of the long bones were closed.

Examination of the seminal specimen, which consisted of a few drops of fluid, showed no spermatozoa present.

The urinary hormone data included a 17 ketosteroid excretion of 18.4 milligrams per 24 hours and a gonadotropin excretion of 60 rat uterine units, 35 rat ovarian units, and 7 rat corpora lutea units per 24 hours.

Histological studies of the biopsy tissue from the testes showed that the normal testicular architecture was entirely lost: the tissue consisted of irregular areas of condensed stroma in which the remnants

of seminiferous tubules remained visible as thickened, hyalinized basement membranes surrounding lumens filled with débris or occasionally, with a few Sertoli cells. Some small, homogeneous areas indicated the site of completely degenerated tubules. The stroma contained many engorged vessels of all sizes which were in close proximity, indicating condensation. There was massive nodular, as well as medullary, hyperplasia of the Leydig cells (Fig. 3a). In some areas these cells were distributed diffusely in large numbers among the other stromal elements; elsewhere discrete nodules surrounded by concentrically flattened and compressed cells were present. The largest of these nodules measured 0.8 millimeter in diameter and was visible easily with the naked eye. The Leydig cells, which were scattered diffusely throughout the tissue, were generally of normal size with pale, foamy cytoplasm and round or oval, vesicular nuclei. No lipofuscin or crystalloids were seen (Fig. 3b). On the other hand, the cells within the hyperplastic nodules had a far different appearance: There was no longer a uniformity of cell size, for many of the Leydig cells were very large and some of their nuclei were almost double normal size. An occasional foamy or almost clear cell could be seen, but the vast majority showed an intense eosinophilia, sometimes with a narrow clear zone at the extreme periphery of the cytoplasm (Fig. 3c). With the Masson stain the cytoplasm of these cells varied in color from steel gray to rose violet. Within these hyperplastic nodules numerous blood filled capillaries were present, but no other vascular changes were noted.

In summary, the clinical evidence of hypoandrogenism of this patient consisted of scanty facial and body hair, an adolescent voice, poor physical strength, a small penis, testes, and prostate. The habitus was definitely feminine. Azoospermia was present. Hormone studies showed a 17 ketosteroid output of 18.4 milligrams per day (a value near the upper limits of normal). Despite this value, the gonadotropin output was 60 rat uterine units per day (approximately 6 to 10 times normal excretion and representing the largest value in this entire group of patients). The Leydig cells showed massive, diffuse and nodular hyperplasia. Although a very large proportion of the cells (far more than in patient 1) showed abnormal cytology, the 17 ketosteroid output was near the upper limits of normal. Finally, despite this 17 ketosteroid output and histological evidence of Leydig cell hypertrophy and hyperplasia, clinical signs of androgen deficiency were unmistakable.

Patient 4. This 18 year old college student entered the hospital for the treatment of bilateral gynecomastia.

The clinical history revealed that he had noted the development of a subareolar lump in one breast and 6 months later a similar change occurred in the other breast. The hard nodules had regressed slightly with time. Pubic hair appeared at the age of 16.5 years. He shaved at 17 years and he has shaved once or twice a week since that time. His sexual drive was not very marked.

Physical examination showed a tall slender, gracile build, of somewhat feminine type. There was bilateral gynecomastia with an increase in both glandular and adipose tissue. There was minimal axillary and facial hair and there was almost no body hair. The pubic hair was scanty and of feminine distribution. The penis measured 3.5 inches in length and 3 inches in circumference at the corona. The scrotum was well developed. The testes measured 1.5 by 0.75 by 0.75 inches and were moderately firm. The prostate was small. The height was 70.5 inches, the span was 72.5 inches and the ratio of the upper half to the lower half of the body was 34.5 to 36.0. The weight was 160 pounds.

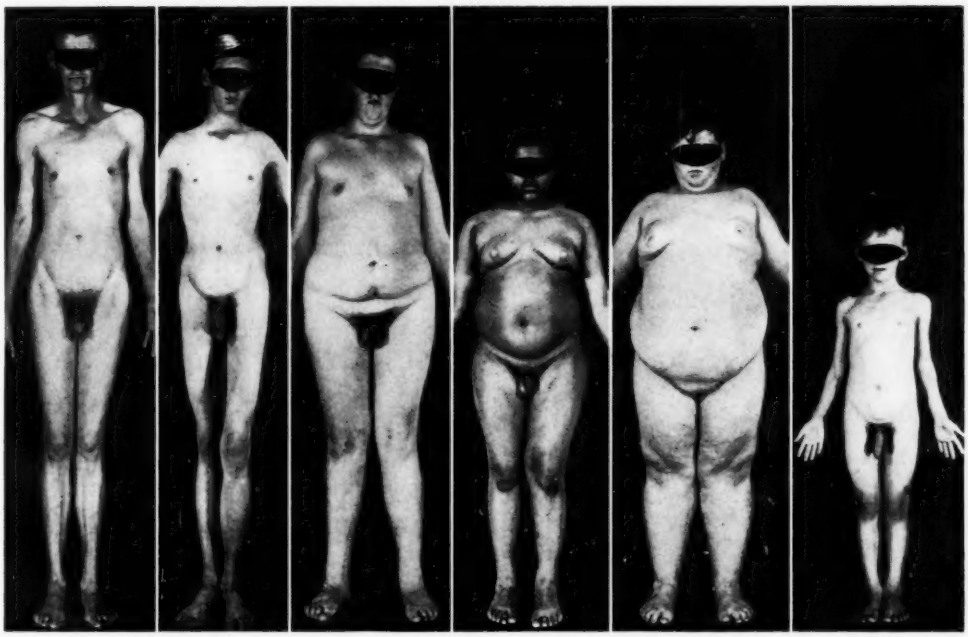
Routine laboratory studies revealed normal blood and urine. The basal metabolic rate was —7 per cent. The sella turcica and sinuses were normal on roentgenologic examination. The osseous age was 15 years.

Examination of the seminal specimen, which was 3 cubic centimeters in volume, showed 19,000,000 spermatozoa per cubic centimeter. Fifty per cent showed normal motility and 72 per cent showed normal morphology.

The urinary hormone data included a 17 ketosteroid excretion of 11.0 milligrams per 24 hours and a gonadotropin excretion of 5 rat uterine units, 5 rat ovarian units, and less than 3 corpora lutea units per 24 hours.

Histological studies of the biopsy specimen from the testes showed that architecture was fairly well preserved (Fig. 3d) although there was a great deal of interstitial hemorrhage and serous exudate. There was no condensation of the stroma and no peritubular fibrosis. A few completely hyalinized tubules and some areas of incipient hyalinization were seen, but for the most part the basement membranes were thin and delicate. The Sertoli cells were very prominent due to the scantiness of the spermatogenic cells. All stages of spermatozoal maturation could be seen in some of the other tubules. The Leydig cells occurred in groups which were usually of normal, but sometimes of increased, size; there was no evidence of condensation in these hyperplastic areas (Fig. 3d). Elongated, small transitional cells with homogeneous cytoplasm were fairly numerous. Most of the true Leydig cells had a vacuolated or foamy cytoplasm; they did not show the densely staining, hazy cytoplasm of cells described in patients 1 and 2. No pigment or crystalloids were found within the cells. The nuclei were fairly dense and the nucleoli seldom visible. No vascular changes were observed.

In summary this patient presented a eunuchoid habitus, feminine contour, and bi-



a b c d e f

Fig. 1. a, Patient 1; b, patient 2; c, patient 5; d, patient 6; e, patient 7, f, patient 8.

lateral gynecomastia. Pubic hair appeared late; he shaved infrequently and the body hair was very scanty. The penis was of normal size but the testes and prostate were small. Normal spermatozoa were present in the seminal fluid. The 17 ketosteroid excretion (11 mgm. per day) was at the lower limit of normal; gonadotropin excretion was normal. The testicular biopsy showed a slight increase in the number of Leydig cells and definite regression of the spermatogenic elements even in the absence of elevated gonadotropins.

Patient 5. This 16.5 year old schoolboy entered the hospital because of a slipped femoral epiphysis.

The clinical history showed that he "always" had been overweight and tall for his age. Pubic hair appeared at 13 years. The voice had not changed. Heterosexual interests had not developed.

The physical characteristics are shown in Figure 1c. The blood pressure was 130/90 millimeters of mercury. There was no facial, axillary or body hair, and the pubic hair was scanty and of feminine distribution. The penis measured 2.5 inches in length and 3 inches in circumference at the corona. The testes were 0.5 by 1 by 1 inches and 0.75 by 1 by 1 inches in size. The prostate was small. The height was 70 inches, the span was 74 inches, and the ratio of the upper half to the lower half of the body was 34 to 36. The weight was 232 pounds.

Routine laboratory studies revealed normal blood and urine. The basal metabolic rate was -8 to -11 per cent. The blood sugar was 97 milligrams per cent; the serum cholesterol was 165 milligrams per cent. The sella turcica appeared normal. The osseous age was ± 15 years.

Examination of seminal specimens, which had volumes of 0.5 cubic centimeter, showed total spermatozoal counts of 65,000,000. Ninety-five per cent of the spermatozoa had normal cytology; 50 per cent showed motility; and normal motility was present in 20 per cent.

The urinary hormone data included a 17 ketosteroid excretion of 10.2 milligrams per 24 hours and gonadotropin excretion of less than 2 rat uterine, ovarian or corpora lutea units per 25 hours.

Histological studies of the biopsy tissue from the testes showed that the architecture of the tissue was well preserved. The tubules were normal in size and in many of them all stages of spermatogenesis appeared. Many of the tubules showed a hyalinized basement membrane and in some areas there was an increase in peritubular hyaline connective tissue.

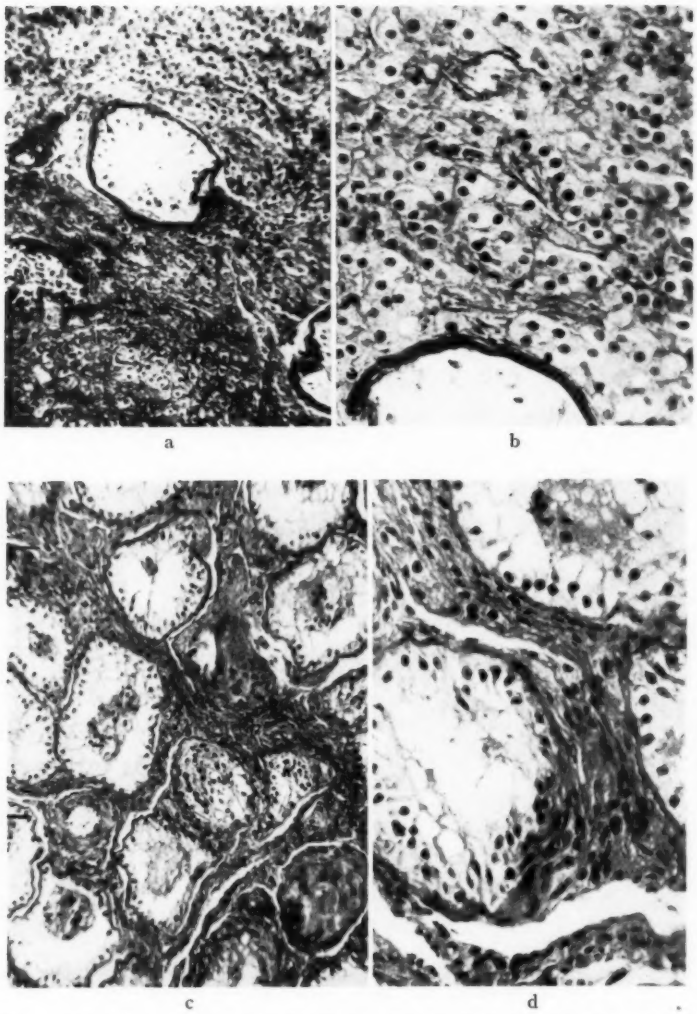


Fig. 2. Photomicrographs of testicular tissue. a and b, Patient 1; c and d, patient 2.

Elsewhere, the stroma had a delicately fibrillar character. The universal scarcity of Leydig cells was very remarkable: They appeared, one or two cells at a time, in the areas of loose interstitial tissue; none of the usual small aggregates of cells was seen. The Leydig cells themselves were uniformly small. The cytoplasm was often foamy but sometimes stained a homogeneous pink with eosin. No pigment or crystalloids were present. The nuclei varied from homogeneously dense to vesicular in appearance. No vascular changes were noted.

In summary, this obese patient presented a feminine, eunuchoid habitus, scanty pubic hair, an adolescent voice, small penis, testes and prostate, and decreased seminal volume, motility and total count, although the spermatozoal count per cubic centimeter was normal. Both 17 ketosteroid (10.2 mgm. per day) and gonadotropin excretion (less than 2 rat uterine units per day) were definitely

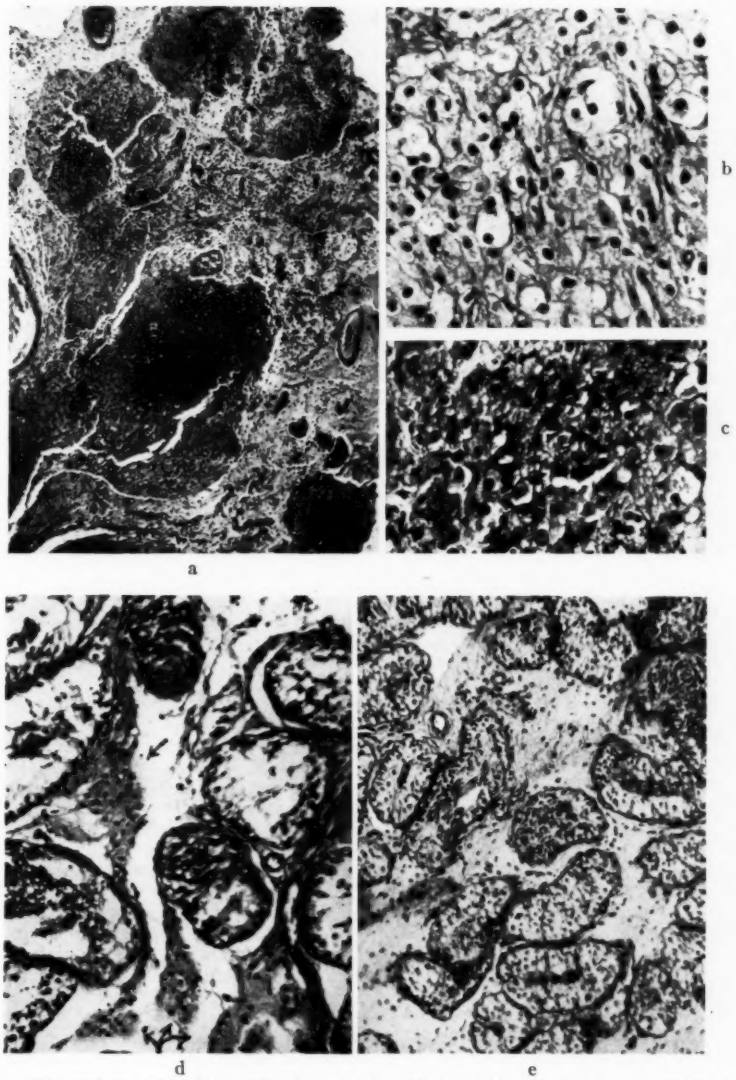


Fig. 3. Photomicrographs of testicular tissue. a, b, and c, Patient 3; d, patient 4; e, patient 7.

low, yet relatively few, small Leydig cells (even with a low gonadotropic stimulation) secreted more 17 ketosteroids than the hyperplastic, overstimulated cells of patient 1.

Patient 6. This 14 year old negro boy consulted the Endocrine Clinic because of a 40 pound weight gain in 6 months.

The clinical history showed that he "always" had been somewhat overweight, and that he had a voracious appetite and a marked craving for sweets. Asthma had been present since the age of 7 years. Pubic hair appeared at 13 years. No erections or nocturnal emissions had been noted. Psychiatric examination was normal.

The physical characteristics are shown in Figure 1d. The blood pressure was 150/90 millimeters of

mercury. The axillary hair was scanty, the pubic hair abundant. There was no facial or body hair. A nodule of glandular tissue about 1.5 inches in diameter was present in the ample fat tissue of each breast. The penis measured 3.5 inches in length and 3.5 inches in circumference at the corona. The scrotum was well developed. The testes measured 1.75 by 1.25 by 1 inches and 2.0 by 1.25 by 1 inches and were of normal consistency. The height was 66.25 inches. The span was 72 inches. The ratio of the upper half to the lower half of the body was 31 to 35.25. The weight was 183 pounds.

Routine laboratory studies revealed normal blood and urine. The basal metabolic rate was +6 and +15 per cent. The visual fields were normal. Skull roentgenograms showed slight bridging of the sella turcica, normal frontal and rudimentary mastoid sinuses. The osseous age was normal.

An epididymal puncture showed an absence of spermatozoa.

The urinary hormone data indicated a 17 ketosteroid excretion of 7.3 milligrams per 24 hours and a gonadotropin excretion of less than 3 rat uterine, ovarian, or corpora lutea units per 24 hours.

Histological studies of the biopsied testes (Fig. 4a) showed that the architecture of the testis was well preserved. The tubules were of normal size, the basement membranes were delicate and of normal thickness save for occasional hyaline areas. Sertoli cells were present in normal numbers but there was a marked decrease in the spermatogenic elements. Small numbers of spermatogonia, occasional spermatocytes, and, in a few tubules, spermatids were noted. The stroma showed a patchy increase in the form of widened bands of intertubular tissue. The stroma, even in these areas, was delicate and fibrillar in character, with the elongated nuclei of fibrocytes being the chief cellular elements. Vesicular nuclei were seen infrequently; the cytoplasm was pale and homogeneous. No pigment or crystalloids were seen, and no vascular changes were observed.

In summary, this obese, eunuchoid negro boy with bilateral gynecomastia developed pubic hair at the usual age. The osseous age, the penis, testes, and scrotum were normal. Azoospermia was present. The 17 ketosteroid excretion was normal for the age and the gonadotropin excretion was low. The testes showed decreased spermatogenesis and infrequent, small Leydig cells. This, then, is the first patient to run true to expectation: low gonadotropins, low-normal 17 ketosteroid excretion, relatively few Leydig cells (but normal-sized testes) and minimal signs of hypoandrogenism. The eunuchoid habitus may have been a racial characteristic.

Patient 7. This 16 year old boy entered the hospital because of obesity and feminine appearance.

The clinical history indicated that the patient had been obese since childhood, weighing 178 pounds at 10 years of age and 287 pounds at 13 years. The voice was high pitched at the age of 16. No body or facial hair had appeared, and no erections or nocturnal emissions had been noted. Increased craving for sweets, polydipsia, and oliguria were present.

The physical characteristics are shown in Figure 1e. The blood pressure was 130/90 millimeters of mercury. Genu valgum and an increased carrying angle at the elbow were noted. There was slight fuzz on the chin and pubis. In addition to abundant adipose tissue, there was a mass of firm glandular tissue about 2 inches in diameter in each breast. The penis measured 3 inches in length and 2.5 inches in circumference at the corona. The scrotum was small. The testes measured 1 by 0.75 by 0.5 inch. The height was 66.25 inches. The span was 67.9 inches. The ratio of the upper half to the lower half of the body was 34 to 32.25. The weight was 299.5 pounds.

Routine laboratory studies revealed normal blood and urine. The basal metabolic rate was +13 per cent. The electroencephalogram was normal, and the intelligence quotient was 84. Visual fields showed questionable concentric narrowing. Roentgenogram of the sella turcica was normal. The osseous age was +10 to −13 years.

A seminal specimen could not be secured.

The urinary hormone data indicated a 17 ketosteroid excretion of 4.7 milligrams per 24 hours and a gonadotropin excretion of less than 3 rat uterine, ovarian, or corpora lutea units per 24 hours.

The histological studies of the biopsied testes showed that the architecture was somewhat unusual: The tubules were uniformly small in size and the connective tissue was prominent and rather condensed, as if all the structures had decreased in size (Fig. 3e) There was some increase in the peritubular connective tissue and the basement membranes of the tubules had a highly refractile appearance, resembling somewhat the elastica interna of an artery (Fig. 4c). The seminiferous apparatus consisted chiefly of Sertoli cells although spermatogonia and occasional spermatocytes were present. Most of the tubules were solid cords of cells, with masses of amorphous débris or cellular material, in place of a lumen; very rarely a tubule with a true lumen was seen. The stroma was increased throughout, and varied from a loose areolar network to fairly dense, hyaline strands. The stromal cells were chiefly mature fibrocytes although some had vesicular nuclei. Fibroblasts were present in the areas of loose connective tissue. There were no cells which could be identified as Leydig cells. The largest vesicular nuclei were not associated with cells having definite boundaries or distinct cytoplasm. No vascular lesions were observed.

In summary, this very obese boy of somewhat feminine habitus showed a delay in the development of genital hair, a high pitched voice, gynecomastia, retarded ossification, a

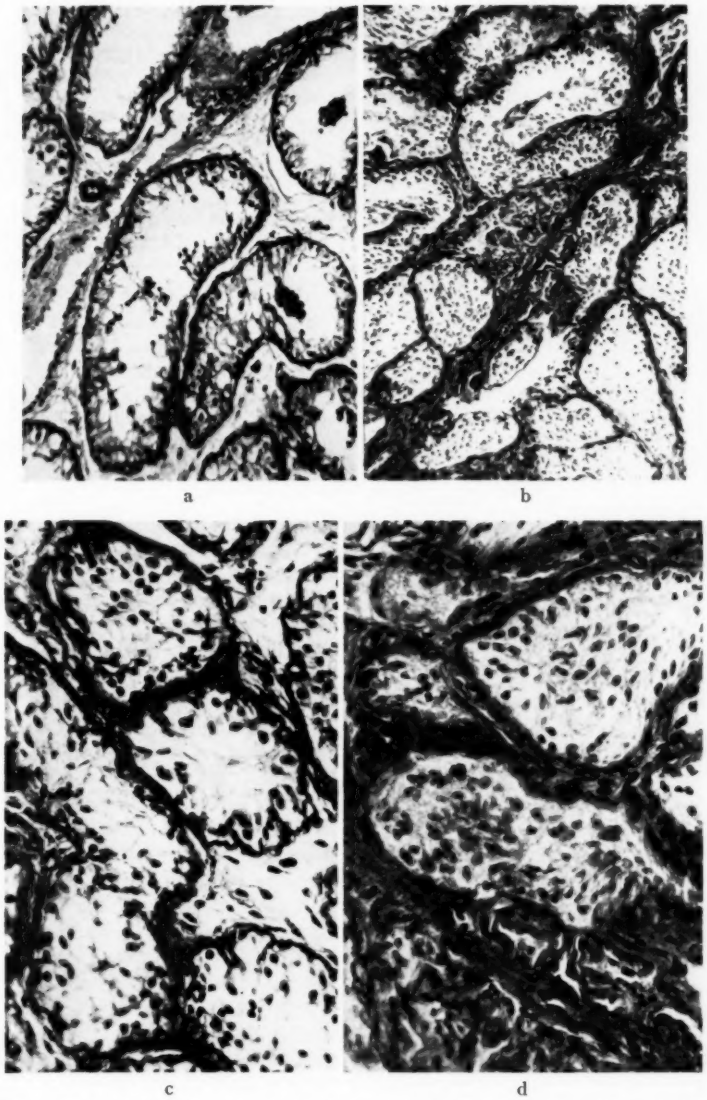


Fig. 4. Photomicrographs of testicular tissue. a and c, Patient 6; b and d, patient 8.

penis of normal size, small testes, and azoospermia. The 17 ketosteroid excretion was very low (4.7 mgm. per day) and the gonadotropin excretion was also low. Extremely few Leydig cells were present. This patient also runs true to expectation (i.e., atrophy of the Leydig cells, low gonadotropins and low 17 ketosteroids, probably entirely of adrenal origin). Under these circumstances the presence of bilateral gynecomastia is rather remarkable and it does not seem very likely that the hypofunctional testes should be held re-

sponsible. The presence of a normal-sized penis and of clinical evidences of hypoandrogenism is worthy of note (see patient 2).

Patient 8. This 6.5 year old boy entered the hospital because of precocious statural and sexual development which was noted approximately 1.5 years previously.

The clinical history showed that he "always" had been a "precocious" child; however, enlargement of the penis was not observed until the age of 5 years. Pubic and axillary hair and acne appeared at the age of 6 years. No voice changes were noted and there was no unusual sexual activity. During the observation, his growth was as follows: At 6.5 years, the height was 52 inches; the span was 51 inches and the ratio of the upper to the lower half of the body was 27 to 25. The weight was 59 pounds. At 7 years, the height was 54 inches; the weight was 65 pounds. At 8 years, the height was 57.25 inches; the span was 57 inches; and the ratio of the upper to the lower half of the body was 29 to 28.25. The weight was 78 pounds. His voice changed at 8 years.

The physical characteristics are shown in Figure 1f. There was no facial hair, but acne was present over the forehead, chin, and nuchal regions. There was moderate axillary and pubic hair. The penis measured 4.5 inches in length and 3.5 inches in circumference at the corona. The scrotum was small. The testes measured 1.0 by 0.5 by 0.5 inch. The prostate was compatible with the penile size.

Routine laboratory studies revealed normal blood and urine, save for a red blood cell count of 5.6 million. The basal metabolic rate was −4 per cent. The glucose tolerance curve was: fasting, 82 milligrams per cent; 0.5 hour, 105 milligrams per cent; 1 hour, 127 milligrams per cent; 2 hours, 115 milligrams per cent; 3 hours, 115 milligrams per cent; 4 hours, 112 milligrams per cent. The blood chlorides were 592 milligrams per cent. The serum sodium was 114 milliequivalents per liter and the serum potassium was 4.0 milliequivalents per liter. The visual fields were normal. Intravenous urograms were normal. A roentgenogram of the sella turcica appeared normal. The frontal sinuses were absent at 6.5 years and present at 8 years. The osseous age was +10 to −13.

An epididymal puncture yielded no spermatozoa.

The urinary hormone data indicated a 17 ketosteroid excretion of 7.3 milligrams per 24 hours (normal values 2 to 4 milligrams per 24 hours) and a gonadotropin excretion of 20 rat uterine units per 24 hours.

Histological studies of the biopsied testes showed that the architecture of the tissue generally was well preserved (Fig. 4b). Many tubules were immature, but their appearance, size, and number were compatible with the patient's age. The basement membrane was highly refractile and there was slight hyalinization of some of the tubules. The Sertoli cells were numerous and spermatogonia were present in moderate numbers; occasional cells resembling spermatocytes were seen but spermatogenesis did not progress beyond this stage. In a very few tubules degenerative changes of a localized character were present, but not in unusual numbers. Many of the tubules showed no lumens. The stroma was very scanty; in some areas it consisted of a surprisingly dense, hyaline connective tissue and in others of delicate, scattered fibrocytes and fibroblasts. Occasionally, larger, round nuclei, suggestive of Leydig cells, were present, but no fully developed Leydig cells were found (Fig. 4d). There were no aggregates of round nuclei indicative of potential Leydig cell development. No vascular lesions were noted.

In summary, the height, weight, ossification, pubic, leg and axillary hair and penile and prostatic size were greatly advanced. Acne was present. There was, however, no change in the voice, no facial hair, no evidence of sexual activity and no seminal fluid. The 17 ketosteroid output (7.3 mgm. per day) was approximately double the normal value and the gonadotropin excretion was markedly elevated. The histological appearance of the seminiferous tubules and of the Leydig cells was consistent with the patient's age, apparently showing no response to the increased gonadotropin secretion. Androgen production of this patient was apparently extratesticular.

The clinical, homonal, and cytologic findings of these 8 patients are summarized in Table I.

DISCUSSION

Clinical criteria of androgenic deficiency (3). The development of *body hair* is one of the most prominent clinical features of androgenic activity. Although racial and constitutional factors, as well as the activity of the adrenal cortex, play important rôles in determining the amount and distribution of body hair, the time of appearance of body hair yields important evidence of the state of testicular androgen production. In this respect, the hair of the face affords a very sensitive index of androgenic activity: both the amount and distribution, but particularly the time of appearance and rate of growth (easily measured by the frequency of shaving), are important. The characteristics of the facial hair obviously are subject to considerable individual variations.

The *pitch of the voice* and the *age at which the voice changes* are also valuable evidence of an-

TABLE I.—SUMMARY OF CLINICAL, HORMONAL, AND CYTOLOGIC DATA

	Patient 1 Intrinsic hypogonadism (Heller-Nelson type)	Patient 2 Intrinsic hypogonadism (Heller-Nelson type)	Patient 3 Intrinsic hypogonadism (Heller-Nelson type)	Patient 4 Hypogonadism, unqualified	Patient 5 Hypopituitary hypoandrogenism	Patient 6 Hypopituitary hypogonadism	Patient 7 Hypopituitary hypogonadism	Patient 8 Intrinsic hypogonadism and hyperpituitary adrenogenitalism
Deviation in pounds from normal weight	0	−15	0	+20	+110	+75	+180	+20
Eunuchoid habitus	+	+	?	+	+	+	?	0
Feminization	0	0	+	+	+	0	+	0
Size of penis	Normal	++	−	Normal	−	Normal	−	++
Decreased testis size	+++	++	++	+++	+++	0	+++	0
Gynecomastia	0	0	0	+	0	+	+	0
Osseous age		−	Normal	−	Normal	Normal	−	+
Number of Leydig cells	++	+	+++	+	−	−−	−−	−
17 ketosteroids mgm. per 24 hours	6.6	11.3	18.4	11.0	10.2	7.3	4.7	7.3
Gonadotropins rat uterine units per 24 hours.	25	25	60	5	Less than 2	Less than 3	Less than 3	20

drogenic activity, although apparently not quite as sensitive signs as beard growth.

The *body habitus* is the result of complex hormonal phenomena acting over prolonged periods of time. The persistence of juvenile fat distribution is only one feature of androgenic deficiency. Retardation of epiphyseal closure and compensatory pituitary hyperactivity due to the intrinsic testicular failure appear to be the basis for the development of a eunuchoid habitus. Heller and Nelson (5) have shown, however, and we have confirmed their findings, that this hormonologic pattern does not result necessarily in a eunuchoid habitus. In the objective determination of eunuchoid build, we have found that, in the absence of skeletal deformity, the ratio of the upper to the lower half of the body reveals more often eunuchoid proportions than the ratio of height to span. The reason for this is quite obvious: measurement of the upper and lower halves of the body provides a direct comparison between the vertebral column (flat bones) and the long bones, whereas measurements of the height and the span include elements of each bone type (long bones, shoulder girdle, and vertebral column) and therefore, these tend to dilute the anthropometric disproportion. Deformities, as genu valgum and kyphosis, however, will render these measurements misleading unless the disproportion is very marked.

The *size of the penis* is often a very poor criterion of androgenic activity, for rather severe degrees of deficiency may be present before diminutive size becomes significant; furthermore, we have observed patients, with obvious evidence of hypoandrogenism, who have normal or even large penes (patient 2). It is very interesting, however, that increase in penile size is one of the first responses to testosterone therapy.

The *size of the testes* bears only the crudest relationship to the clinical signs of testicular function. A small testis may show large numbers of highly active Leydig cells, or a testis of normal size and consistency may show a great deficiency of hormone-producing tissue.

The *size of the prostate*, being unsuitable for exact measurement can be used only to judge gross deficiencies of androgen production.

Sexual interest, activity, and potency involve far too many psychological factors to be of clinical value in the majority of patients.

Muscular strength, endurance, and stamina also are influenced greatly by psychological factors and should be evaluated with great caution. It is possible that objective measurements may yield worthwhile information especially in the evaluation of treatment of hypoandrogenism.

Other signs of androgen deficiency, as the dry, senile appearance of the skin, muscular cramps, urinary frequency and nocturia,

represent severe degrees of androgen deficiency.

Biochemical criteria of androgen deficiency. The usual urinary hormonal studies provide a poor estimate of testicular function. The 17 ketosteroid excretion may be determined with considerable accuracy, although it involves a long and tedious chemical procedure. However, the data represent the combined 17 ketosteroid output of testes and adrenals. In relating these data to androgen production, one assumes that the androgenic steroids form a more or less constant proportion of the total 17 ketosteroid output. This assumption is likely to be fallacious, especially when a disturbance of the steroid metabolism is suspected. On the other hand, present methods of androgen assay do not permit general clinical usage. The technique of chromatographic analysis has been applied recently to clinical practice; if these data were quantified and correlated with androgenic activity, they would provide a great advance in both qualitative and quantitative studies of steroid excretion.

Criteria of testicular pathology. Most of the careful cytological studies of the Leydig cells have been made in animals, partly because of the availability of material and partly because human autopsy material is frequently unsuitable for studies of the normal state (14). In fact, only within the last decade, has it been realized that the "textbook appearance" of testicular tissue is the exception rather than the rule (17).

There is a number of formidable difficulties in the interpretation of testicular pathology. Measurement of the total volume of tubules or Leydig cells of normal testes has been unsatisfactory, even with the use of planimetric methods; the difficulty of making these estimates in the presence of pathological alterations is much greater (15). Far more important is the fact that there are no specific histochemical techniques for the measurement of hormone production of Leydig cells. The usual cellular stains (hematoxylin-eosin and Masson) reveal nonspecific cytological changes which are extremely difficult of correlation with functional activity. General lipoid stains (Sudan and Nile blue) do not reflect the 17 ketosteroid content of the cells and are generally of little value. Stains for cholesterol-like substances, based on the Liebermann-Burchardt reaction, are more specific, but these are subject to the same criticism and they are often unreliable. The most valuable histochemical methods, apparently, are based on the phenylhydrazine stain of Bennett (12). This method at first was thought to be specific for 17 ketosteroids, but some doubt recently has been expressed in this regard (1). It is unfortunate that this method as yet has not been applied to clinicopathological studies of testicular function.

The presence of the crystalloids of Reinke apparently reflects to some degree the steroid-producing function of the Leydig cells. These odd-shaped bodies which stain with safranine, methyl violet, or other common dyes, give histochemical reactions of globulins, and not those of lipids. Their presence or absence, nevertheless, correlates fairly well with major changes in Leydig cell function.

It is agreed generally that the appearance of mitochondria and of the Golgi apparatus affords valuable evidence on the functional state of a cell. The material obtained by testicular biopsy is suitable for these studies (2), which would provide valuable information.

Descriptions of the histology of the testis (save for its spermatogenic elements) are scattered in the literature and are influenced often by histological studies of other species. Moreover, the criteria of normalcy, especially of the interstitial elements, are poorly defined. It is necessary to describe, therefore, what are considered normal features of some testicular elements (2, 11).

The seminiferous tubules are bounded by a basement membrane which is strengthened by a layer of lamellated connective tissue. Both elastic and collagenous fibrils are present; the width of this band varies from about 1 to 4 microns. Within the tubule, spermatogenic and the Sertoli cells are found. The spermatogenic cells will not be discussed, as detailed descriptions are found in any textbook of histology (11). The Sertoli cells, however, are of considerable interest. The function of these cells is entirely unknown, although they have been thought to be "supporting" or "nutri-

tive" elements, supposition without any foundation of fact. Recently estrogen-producing, Sertoli cell tumors of the testis have been described (9) which may be the first objective evidence of the function of these cells (18).

The seminiferous tubules are supported in a loose stroma composed of collagenous fibrils, blood vessels, nerves, fibroblasts, macrophages, mast cells, and Leydig cells. The Leydig cells are scattered singly or in small groups of 4 to 10 cells throughout the stroma without any relation to tubules or blood vessels. The accumulations of cells, as shown by Klinefelter and associates, should not be regarded as normal and, in fact, were regarded as hyperplasia by the pathologist to whom they were shown. There are also smaller cells which are hard to distinguish from fibroblasts, but their proximity to nests of Leydig cells suggests their developmental potentialities. The Leydig cells themselves are round, irregular or polyhedral in shape, about 14 to 20 microns in size, with a nucleus 5 to 8 microns in diameter, round and usually eccentric. The nuclear chromatin occurs in fine strands or granules and 1 to 3 large nucleoli usually are present. There is an attraction sphere around the nucleus and the Golgi apparatus is found immediately outside this region. Occasional binucleated cells are normally present. The cytoplasm is highly granular and contains numerous lipid globules (especially near the periphery), giving the cell a foamy appearance. Many of these fat globules are filled by nonlipid material with a surface coating of fat. Neutral fats, phosphatids, glycolipids, cholesterol esters, and steroids have been identified in the cytoplasm. There are found also the crystalloids of Reinke which may be seen also in the Sertoli cells. Lipofuscin, a brownish wear-and-tear pigment, appears after adolescence and generally tends to increase with age. Occasionally, smaller cells with dense, chromophile cytoplasm, suggesting transitional forms from fibroblast-like cells, are observed.

With this discussion of normal cytology and of the distribution of Leydig cells in mind, it becomes possible to evaluate the alterations observed in our patients as well as in those of others. There has been an unusual hesitancy to make the differential diagnosis between *hyperplasia* and *condensation of the Leydig cells*, although suitable criteria for this differentiation have long been established by pathologists.

Condensation implies the loss of parenchyma; the stroma does not disappear in proportion and there remain residual structures, as an increased number of blood vessels, which are closer together than usual. One expects to find also remnants of degenerated tubules, which do not disappear entirely but leave dense, hyalinized discs at their previous sites. With the collapse of the stroma, groups of Leydig cells are brought into closer proximity. These aggregates should have an alveolar type of structure with islands of irregular size and shape which are separated by variable amounts of stroma. In lesser degrees of condensation, where these changes are not so marked, the irregular distribution of the reticulum fibrils is evident and is quite different from the regular and even distribution of hyperplasia. Moreover, it is manifestly impossible to consider unusually large aggregates of Leydig cells as condensation phenomena when they are embedded in loose areolar tissue (Fig. 3d).

Hyperplasia may be of diffuse or nodular variety (Figs. 2a and 3a). The former type develops from an overgrowth of the normal pattern with gradual coalescence of the groups to form a medullary cell mass with a delicate reticulum and very scanty stroma. There is obviously no difficulty in distinguishing this from condensation phenomena. With stronger, irregular proliferation, nodular conformations may appear. These also are differentiated easily from condensations because the stroma within the nodule is delicate and homogeneous instead of irregular and strand-like, and because the tissues of the periphery often will show signs of compression, as concentric flattening of the adjacent stroma and parenchyma. The coexistence of condensation and hyperplasia is seen (Fig. 3a), and there has been no difficulty in distinguishing the two. We have felt, therefore, that it is wise to abstain from nonspecific terms, as "clumping." The differentiation of condensation and hyperplasia is of great functional significance and every effort should be made to distinguish the two.

SUMMARY

In these 8 patients we have observed some agreement and many discrepancies between the expected and the observed findings. These may be summarized as follows:

1. Leydig cells and hormone excretion. Increased numbers of Leydig cells were associated with low (patient 1) or high (patient 3) 17 ketosteroid excretion, or with normal (patient 4) or high (patients 1, 2, 3) gonadotropin excretion. Decreased numbers of Leydig cells were associated with very low (patient 7), low normal (patient 5), or high (patient 8) 17 ketosteroid excretion and with low (patients 6, 7) or high (patient 8) gonadotropin excretion. We confirm, therefore, the observation of Heller and Nelson (5) that there is no quantitative correlation between elevation of gonadotropic excretion and the 17 ketosteroid output.

2. Clinical symptomatology. Clinical evidence of hypoandrogenism was observed in the presence of low (patient 1) or high (patient 3) 17 ketosteroid excretion. Eunuchoid habitus was present with high (patients 1, 2), normal (patient 4) or low (patient 5) gonadotropin excretion or with increased (patient 1) or decreased (patient 6) numbers of Leydig cells. A large penis was noted with low normal (patient 2) or high (patient 8) 17 ketosteroids and a small penis with high normal 17 ketosteroids (patient 3).

Evidence of feminization was observed with high normal 17 ketosteroids and increased numbers of Leydig cells (patient 3), with low normal 17 ketosteroids (patients 4, 5) and with low 17 ketosteroids and few Leydig cells (patient 7).

Gynecomastia was observed in the presence of increased (patient 4) or greatly decreased (patients 6, 7) numbers of Leydig cells, and yet with normal sized penis (patient 6). It was seen with normal (patient 4) or low (patients 6, 7) gonadotropin excretion or with low normal (patient 4) or low (patient 7) 17 ketosteroid excretion.

CONCLUSIONS

These 8 selected patients illustrate notable discrepancies between clinical evidence of androgenic activity, urinary hormone excretion, and testicular histology.

Alterations of the Leydig cells, as hypertrophy or hyperplasia *per se*, cannot be regarded as indicative of increased or even of normal secretory activity. It is possible that studies of mitochondria and Golgi apparatus, as well as the use of perfected histochemical techniques may provide in the future adequate cytologic criteria of endocrine cellular activity.

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A COMPARATIVE STUDY OF THROMBOANGIITIS OBLITERANS IN WHITE AND NEGRO PATIENTS

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SINCE the appearance of the original studies of Buerger in 1907 concerning thromboangiitis obliterans, much has been written concerning this disease. It was believed at first to occur almost exclusively in Russian Jews, but it has since been seen in patients of varied racial origin.

The impression is widespread that this disease is rare in the negro, and this would appear to be confirmed by the small number of cases of this disease in the negro which have been recorded in the literature. Our interest in this subject was aroused when we encountered an instance of thromboangiitis obliterans in a negro woman. Because this is the first time that this disease has been observed in a female negro, we shall describe later in this paper the salient clinical features presented by this patient. In addition to this, however, the purpose of the present paper is to present a comparative study of thromboangiitis obliterans in white and in negro patients in a large general hospital in which the numbers of admissions of white and negro patients are approximately equal.

REVIEW OF THE LITERATURE

Gemmil (1925) was the first to report thromboangiitis obliterans in the negro race. His patient was a male. Since no pathologic studies were presented, the diagnosis must be considered as presumptive rather than proved.

In 1936 Smith reported a case of this disease in a male negro aged 39 years. The patient's Wassermann reaction was negative. Smith described no pathologic studies so that the diagnosis must be considered presumptive rather than proved.

Parsons in the same year (1936) also recorded the occurrence of this disease in a male negro in whom there was a considerable admixture of white blood. In this patient there was also a history of luetic infection. Parsons stressed the difficulty of distinguishing thromboangiitis obliterans from syphilitic endarteritis obliterans.

Scupham (1936) observed this disease in a male negro but he did not present adequate details concerning his patient.

Yater (1937) described the occurrence of thromboangiitis obliterans in 5 male negroes. All the patients either had syphilis or had a history of a previous luetic infection. Two of Yater's patients required an amputation below the knee, and in the other 3 patients biopsies of the dorsalis pedis vessels were carried out. His patients all presented definite clinical and arteriographic evidences of occlusive peripheral vascular disease.

In 1941 Warshawsky pointed out that in all of the previously recorded cases in negroes there was a considerable likelihood of racial mixing with the white race. He described a case of thromboangiitis obliterans in a full-blooded negro male and accompanied his paper with convincing pathologic studies. Finally, his patient presented no clinical or serological evidences of, and gave no history of having had, syphilis.

To summarize, therefore, 10 cases of thromboangiitis obliterans in the negro have been recorded in the literature. All these patients were males. In 6 of the 10 patients the diagnosis was confirmed by pathologic studies. In 2 of the 10 patients there was no evidence of the presence of syphilis. Only 1 patient, however, could be considered to be a full-blooded negro.

THE RELATIVE INCIDENCE OF THE DISEASE IN WHITE AND NEGRO PATIENTS

Our report is concerned with a group of white and negro patients who were seen in the

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Charity Hospital of Louisiana in New Orleans during a 15 year period extending from 1931 to 1945, inclusive. All patients over the age of 49 years were excluded from this series because of the increasing incidence of other forms of peripheral vascular disease in patients above this age. During this time there were 64 patients in whom the clinical or pathological diagnosis of thromboangiitis obliterans was made. Of these, the diagnosis was made only on clinical findings in 48 patients and a clinical and pathological diagnosis in 16 patients. Of the 48 patients in whom the clinical diagnosis was made, 40 were white men; 3 were white women, and 5 were male negroes. Of the 16 patients in whom the clinical diagnosis was confirmed by pathological studies of the blood vessels, 12 were white men; 3 were male negroes, and 1 was a female negro. In this group of pathologically proved cases the ratio of negro to white patients was 1 : 3. In the entire series in this study there were 9 negro patients and 55 white patients which gives a ratio of 1 : 6.1.

COMPARISON OF AGE INCIDENCE

Forty-nine of the white patients were aged 30 to 49 years while in 6 the disease commenced between the ages of 20 to 29 years. In the negro patients 6 of the 9 patients were 30 to 49 years old and only 3 patients were 20 to 29 years old. However, a statistical analysis was carried out in order to determine whether or not there was a significant difference in the age incidence between the white and negro patients. Examination of the statistics by the X^2 test[1] with Yates' modification showed no significant difference in the age incidence between the two groups.

DURATION OF SYMPTOMS

In order to determine whether or not the duration of symptoms was different in the two groups an analysis was made and showed that in the majority of the white patients (36) the duration of the symptoms was 5 years or less. In 19 of the 55 white patients the duration of symptoms was more than 5 years. Of the 9 negro patients 7 showed a duration of symptoms for 5 years or less while in only 2 of the 9 had the disease lasted longer than 5 years. Again, application of the X^2 test with Yates' modification to the data revealed no significant difference between the two groups in duration of the symptoms and signs of this disease.

[1]Chi square test.

COMPARISON OF RESPONSE TO TREATMENT IN WHITE AND NEGRO PATIENTS

In the 55 white patients, conservative treatment was successful in 31 while it was necessary to perform major amputations of extremities in 19 patients and minor amputations in 5 patients. Of the 9 negro patients, major amputations were performed in 2, minor amputations in 6, while in only 1 patient was conservative treatment successful. When the patients requiring major and minor amputations—24 whites and 8 negroes—were placed in one group and those responding to conservative treatment in a second group—31 whites and 1 negro—comparison of the white and negro patients produced an interesting result. It was determined by means of the X^2 test with Yates' modification that a significant difference existed in this respect between the negro and white patients and that significantly more amputations were required in the negro patients than were required in the white patients with thromboangiitis obliterans. Was the proportion of minor amputations in the negro patients larger than that in the white patients? This question is answered by means of the X^2 test with Yates' modification. This test indicates that the number of minor amputations is very significantly higher in negro patients (6 patients) than it is in white patients (5 patients).

Conversely, the X^2 (Chi square) test with Yates' modification indicates that there is a significantly higher ratio of major amputations to minor amputations in the white patients (19 patients) than in the negro patients (2 patients) in the present series. In comparing the success of conservative treatment and the need for surgical treatment in white and negro patients it was of interest to add to our series of negro patients the 9 negroes recorded in the literature on whom sufficient data were available. When the X^2 test with Yates' modification was applied to the data, our observation

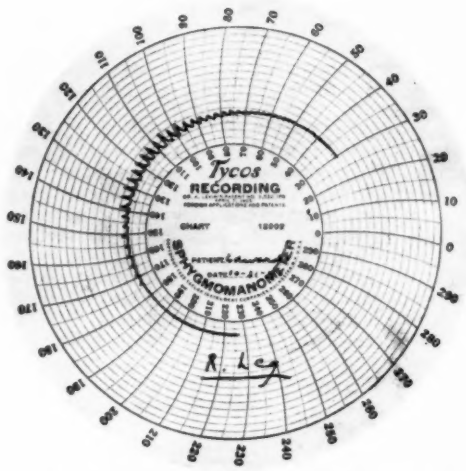

Fig. 1. Oscillogram of right leg showing arterial pulsation.

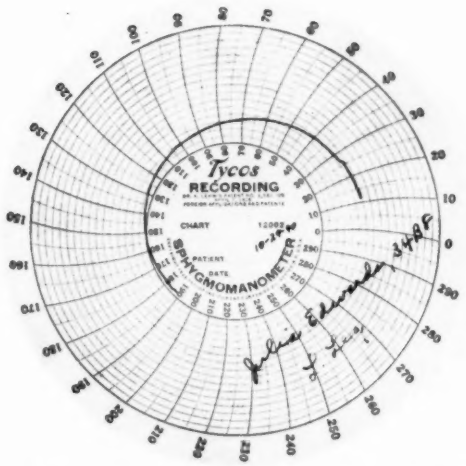

Fig. 2. Oscillogram of left leg (prior to amputation). There is an absence of arterial pulsation.

that the response of negro patients with this disease to conservative treatment is poorer than that of the white patients was confirmed. It was noteworthy that the incidence of major and minor amputations was significantly higher in negro patients than in white patients suffering from thromboangiitis obliterans. The possible reasons for these differences in response to treatment between the two groups of patients will be discussed later.

Because no case report of thromboangiitis obliterans in a female negro has appeared in the literature, we believe that a detailed record of this disease as observed by one of us (H. A. D.) in a negro female would be of interest.

CASE REPORT

J. E., Hospital No. L-40-54467, a negro woman aged 34 years, was admitted to the Charity Hospital of Louisiana in New Orleans in 1940. Her chief complaint was pain in the left leg. Her present illness started 4 years previously when the patient noted an intermittent pain in the left lower extremity. This pain was of a claudication type and increased when the extremity was used. At first the pain was relieved on rest but later the pain became continuous. Three years before admission, the great toe of the left foot became gangrenous and had to be amputated. Three months before admission the patient's left leg felt cold and numb and became the site of a burning pain. These symptoms became progressively more severe, and, finally, there appeared a bluish discoloration of the toes and dorsum of the left foot.

A review of symptoms referable to other systems revealed the presence occasionally of precordial pain and slight dyspnea on exertion. During the past 3 months she had noted epigastric distress which occurred after meals. The patient stated that she vomited two or three times weekly. In her past

Fig. 3. Lateral roentgenogram of left leg. There is no evidence of calcification of the walls of the blood vessels.

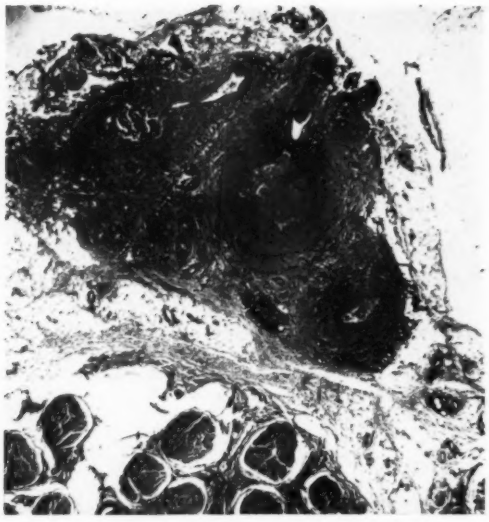

Fig. 4. Cross section of the left posterior tibial nerve, shows thrombosis of the arteries and veins with recanalization. Perivascular fibrosis. ×32. Hematoxylin and eosin stain.

history no serious illnesses were recorded. The patient denied having had syphilis although she admits that she may have had gonorrhea 1 year prior to the present admission. Her family history was noncontributory. The patient was unmarried but had been pregnant three times all of the pregnancies terminating in miscarriages. This suggests the possibility that the patient may have had syphilis. The social history of the patient contained some interesting facts. The patient was a heavy smoker having commenced smoking at the age of 13 years. The patient did not appear to be a full-blooded negro her skin being of a light chocolate color. Further inquiry, however, elicited from her the statement that her grandmother on the maternal side had been a white woman.

Physical examination revealed her temperature to be 98.6 degrees F., pulse rate, 90 per minute; respiratory rate, 20 per minute, and the blood pressure, 140/80.

The patient was a well developed, well nourished negro woman of the stated age who did not appear to be acutely ill. The patient was complaining of pain in the left foot. Examination of the head, eyes, ears, nose and throat was negative. Her dental hygiene was good. The breasts exhibited no abnormalities. The lungs disclosed no unusual findings on physical examination. The heart was not enlarged; its rhythm was regular, and no murmurs could be heard. Abdominal examination revealed a slightly scaphoid abdomen but, otherwise, no abnormal findings. The pelvic organs were not examined.

The upper extremities did not present any abnormal physical findings. The right lower extremity was apparently normal. The pulsations of the right dorsalis pedis and right posterior tibial arteries were strong. The skin of the right extremity was found to be warm.

The most significant physical findings were present in the left lower extremity. The entire left leg was cold, and this coldness of the skin extended half way up the thigh. The second and third toes of the left foot exhibited a bluish discoloration and appeared to be firm and somewhat mummified in appearance. The great toe of the left foot was absent, and at its site there was the healed scar of a previous operation measuring approximately 6 centimeters in length. An irregular superficial ulcer measuring 2.5 centimeters in its greatest diameter and having a dry pink-colored base was present on the dorsum of the foot immediately above the toes. The pulsations in the left dorsalis pedis and left posterior tibial arteries could not be palpated.

Oscillograms of the upper and lower extremities were made. The tracings obtained from the right and left arms were essentially normal and showed no significant differences. The oscillograms of the lower extremities were taken at the midpoint of the calf and at the midpoint of the thigh. The oscillogram of the right leg (Fig. 1) and right thigh revealed good pulsation of the blood vessels with fair amplitude of the waves. However, the oscillogram of the left leg exhibited a complete absence of pulsations (Fig. 2). The oscillogram of the left thigh presented a decreased amplitude of the waves when compared with the oscillogram of the right thigh. Lateral roentgenograms of both lower extremities showed no evidence of calcification of the walls of the arteries (Fig. 3).

Laboratory findings. The hemoglobin value of the blood was 80 per cent. The red blood cell count was 4,200,000 per cubic millimeter. The white blood cell count was 13,013 per cubic millimeter. The differential count was 67 per cent polymorphonuclear leucocytes, 26 per cent lymphocytes, and 7 per cent monocytes. Urinalysis disclosed no abnormal findings. Urea nitrogen content of the blood was 7.7 milligrams per cent.

The flocculation and the Kolmer complement fixation tests were negative. The cerebrospinal fluid—Wassermann reaction—was negative. The cerebrospinal fluid was normal in all other respects.

Gastric analysis showed no occult blood. Free hydrochloric acid, 10; total acidity, 40.

Electrocardiogram showed no definite evidence of myocardial disease.

The clinical diagnosis was (1) thromboangiitis obliterans involving the left lower extremity, (2) pylorospasm.

October 24, 1940. The patient was admitted to the medical service.

October 29, 1940. The patient was transferred to the surgical service.

October 30, 1940. Left lumbar sympathetic block was carried out resulting in immediate warming of

the skin of the left foot. The pulsations in the left dorsalis pedis artery became palpable for the first time. Repeated sympathetic blocks were done over a period of 2 weeks.

November 14, 1940. The gangrene was extending to the dorsum of the foot.

November 16, 1940. Under spinal anesthesia an amputation was carried out below the knee at the junction of the middle and upper ⅓ of the leg. Bleeding was not excessive although a tourniquet was not applied.

December 21, 1940. The wound was completely healed and the patient was discharged.

Pathological study. A dissection of the surgical specimen was performed. It was observed that the anterior tibial, the posterior tibial, and the peroneal blood vessels were thrombosed. The arteries, veins, and nerves were closely bound together by adhesions which appeared to be inflammatory in origin. The arteries were dissected out along their entire length but, even after thorough examination was carried out, disclosed no gross evidences of calcification of their walls.

Microscopic examination. Tissue sections were made at several levels through the tibial artery and vein of the amputated leg. Microscopic examination of the vessels at low magnification (Fig. 4) reveals that all the vessels are occluded by organized thrombi in which can be seen newly developed vascular channels. The vessels are bound together by dense fibrous connective tissue containing numerous lymphocytes, plasma cells, monocytes, and foci of polymorphonuclear leucocytes. A striking feature of the microscopic picture was the appearance of numerous smaller blood vessels suggesting the development of a collateral circulation as a result of occlusion of the larger vessels. The internal elastic lamina of the arteries appeared to be intact. Microscopic examination at a higher magnification (Fig. 5) of the tibial artery showed the presence in its lumen of a cellular well organized thrombus infiltrated by lymphocytes, plasma cells, and other mononuclear cells. The thrombus contained numerous endothelial lined spaces some of which contained fresh blood cells. The internal elastic lamina was intact. The media was somewhat fibrotic and was infiltrated to a moderate extent by mononuclear cells, mainly lymphocytes and plasma cells.

Follow-up. The follow-up of this patient presents points of interest. Two years after her operation she was operated upon for a typical duodenal ulcer, proved by roentgenograms and at operation when a subtotal gastric resection was performed. On being questioned at this time the patient admitted that she had stopped smoking for several months after the amputation of her left leg but had resumed the habit. At the time of her admission to the hospital for treatment of the duodenal ulcer she was smoking 10 to 20 cigarettes each day. She had no symptoms of pain in the stump of her left leg nor in the right leg, examination of which disclosed normally pulsating peripheral arteries.

Fig. 5. Cross section of the left posterior artery, shows organized thrombosis with recanalization and infiltration by mononuclear cells. ×80. Hematoxylin and eosin stain.

ABSTRACTED CASE HISTORIES

It might be pertinent at this point to present briefly the findings in the male negroes who had thromboangiitis obliterans and in whom the diagnosis was proved by means of pathological examination of the surgically removed tissues.

1. F. M., 29 years, male, negro, had pain in right calf; the right foot became gangrenous; there was absence of pulsation of the right popliteal artery; Wassermann reaction was negative, and he gave no history of luetic infection. The patient was a smoker; the right leg was amputated.

Pathological diagnosis: thromboangiitis obliterans.

2. A. D., 26 years, male, negro, had pain in right great toe. Wassermann reaction was negative and there was no luetic history; the patient was a smoker; right great toe was amputated. Pathological diagnosis: thromboangiitis obliterans.

3. P. P., 36 years, male, negro, had pain in right and left lower extremities and upper extremities. He was a smoker. Wassermann reaction was negative and there was no luetic history. He was repeatedly admitted to hospital when he had successive amputations of 5th toe of left foot (1933); the great toe of the right foot (1939), and the index finger of the right hand (1940). Pathological diagnosis: thromboangiitis obliterans.

The 5 negroes in whom only a clinical diagnosis of thromboangiitis obliterans was made might be briefly described.

1. L. J., 31 years, male negro, had pain in the left great toe with gangrene; amputation of toe. Wassermann reaction was negative and he gave no history of lues. Pathologic studies were inconclusive.

2. J. H., 39 years, male negro, had pain followed by gangrene of the 5th toe of right foot requiring amputation. No pathological studies were made. Wassermann reaction was negative but there was a history of luetic infection.

3. C. P., 40 years, male negro, had pain and edema of left lower extremity. He recovered under conservative therapy. No pathological studies were made.

4. O. F., 40 years, male negro, had pain and later gangrene of left lower extremity. Bilateral lumbar sympathectomy was done. Right great toe was amputated. No pathological studies were made. Wassermann reaction was negative and he gave no history of luetic infection.

5. C. R., 28 years, male negro, had pain in left lower extremities. There was absence of pulsation in left dorsalis pedis and posterior tibial arteries; gangrene of 3rd, 4th, and 5th toes of left foot required amputation of these toes. Wassermann reaction was negative. The pathological studies were inconclusive.

A survey of the literature on thromboangiitis obliterans might suggest that this disease is extremely rare in negroes because up to the time of the present report only 10 instances of the disease have been recorded in the negro. In 6 of the 10 patients the diagnosis was confirmed by pathologic studies. In the present series, 9 patients were negroes and in 4 pathological examination of the tissues verified the clinical diagnosis of thromboangiitis obliterans. The fact that 9 of the 64 patients observed during a 15 year period were negroes suggests that the disease is by no means rare in this race.

What is the etiological significance of syphilis in the production of these vascular changes in the negro? In 8 of the 10 instances of thromboangiitis obliterans in negroes previously reported in the literature, syphilis was present. In 7 of the 9 negro patients with thromboangiitis obliterans in this present series there were no serological or clinical evidence of luetic infection and no history of luetic infection. One patient gave a history of having had a syphilitic chancre and a second patient (J. E.) had had 3 miscarriages. We agree with Yater in his conclusion that in view of the high incidence of lues in the negro race the association of this disease with thromboangiitis obliterans in the negro is coincidental.

No significant differences in the age incidence and in the duration of the disease existed between the white patients and the negro patients.

The outstanding difference between the two groups lay in their response to treatment. Conservative treatment, that is, nonsurgical treatment, was conspicuously less successful in negro than in white patients. The incidence of amputations was significantly higher in negro patients than in white. This lack of success of conservative methods of treatment in these patients was noteworthy and may be explained in several different ways.

1. The negro patient comes to the physician later for treatment than does the white patient. However, this contention is not supported by a comparison of the duration of the symptoms in both groups. No significant differences were observed in this respect in the two groups.

2. The greater lack of cleanliness among negro patients may predispose to infection of the poorly vascularized tissues.

3. A comparison of the smoking habits of these negro and white patients was not possible in this study.

4. There may be a racial lack of resistance to this disease in the negro. If this were so, the disease should occur more frequently than it does in this race. Indeed, there is some evidence that the opposite may be true, namely, that some degree of racial immunity to Buerger's disease may exist among negroes. Two facts would tend to support this view. First, the disease is less common in negroes. Second, in the present series of cases the incidence of minor amputations was significantly higher in the negro patients than in the white patients when compared with the incidence of major amputations.

SUMMARY AND CONCLUSIONS

A study is presented of 64 patients suffering from thromboangiitis obliterans. In 16 of these patients the diagnosis was confirmed not only clinically but also by pathological examination of the tissues. Twelve of the 16 patients were

white men, 3 were negro men, and 1 was a negro woman.

No significant differences were observed between the two groups with respect to the age incidence or to the duration of symptoms.

The response to conservative treatment was poorer in the negro patients than it was in the white. The reasons for this difference have been discussed.

The occurrence of thromboangiitis obliterans in a female negro is reported for the first time in medical literature. The clinical diagnosis in this patient was confirmed by pathological studies of the tissues.

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A REPORT ON THE USE OF THE HARRIS TUBE

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SINCE the appearance of Harris' article describing his ingenious tube and his experiences with it as an instrument for decompression of the bowel, there has not to our knowledge been sufficient trial of his tube. In the absence of more recent accounts by others, we felt that it would be of interest to report our early experiences with the Harris tube at the Massachusetts General Hospital.

The present report consists not of a selected number of cases, but, on the contrary, is an account of the first 30 cases in which we used the Harris type of intestinal suction.

We have to date been unable to obtain radio-opaque rubber tubing and have resorted to "koroseal" transparent plastic tubing 3/16 inch in diameter. This tubing can be visualized on a dry x-ray plate, but is not visible by fluoroscopy. Its transparency is an aid to checking its function. The leading end is fitted with a hollow perforated metal tip[1] and a double thickness of condom is tied over this with two fine silk or cotton threads. After the mercury is introduced inside the inner bag and all the air is expressed, the other ends of the bags are similarly tied over an internal metal collar[2] placed 5 inches proximally in the tube. Six small holes about 3/32 of an inch in diameter are then cut out of the side of the tube, with a pair of scissors, an inch apart just above the bag, and the tube is ready for use. The unsalvageable parts of the tube cost 35 cents. We replace the tubing and the bags before reusing the apparatus. A double thickness bag has been resorted to following the accidents reported in Cases 5 and 6. Since using a double-thickness bag we have had no more ruptures with escape of mercury. Four cubic centimeters of mercury were used in most cases, but we have had equal success with 2 and with 3 cubic centimeters.

We have employed the tube in the following manner. Surgical lubricating jelly is used, because mineral oil tends to weaken the rubber bag, and the tube is passed through the nostril into the stomach and then left to progress at will. Mineral oil on the tubing at the nose level adds comfort to the patient and allows the tube to pass more freely. We have not found it necessary to place the patient on the right side or to feed the tube manually. The tube, if left oiled and unattached at the nostril, has progressed of its own accord. Suction has been used only on the obstructed patients, and dietary restriction only when indicated clinically.

If the tube has failed to progress in the first 12 hours, we have used fluoroscopy to place the tip of the tube accurately at the pylorus. It has been our experience that if the tube has not passed the pylorus of its own accord, manipulation under the fluoroscope is also unsuccessful; however, placing the tip of the tube at the pylorus is often rapidly followed by spontaneous passage into the duodenum.

Strapping the tube to the nose has always halted the progress of the tube, and removal of the tube has not been more difficult than when a double-lumen tube has been used. Cases 1 and 4 are interesting in this regard.

The table summarizes the results in the first 30 cases in which we employed this tube. We would like to state here that in only 2, or 7 per cent, of these 30 cases did the tube definitely fail to pass the pylorus within 24 hours and that at operation or at postmortem examination an adequate mechanical cause for failure was present in each case.

In 2 other cases the tube passed the pylorus only to be regurgitated later. Hiccoughing, Trendelenburg position, and pulling on the tube by the patient were thought to be partially or completely responsible for these fail-

From the Surgical Services of the Massachusetts General Hospital.

[1] The metal tip of a Miller-Abbott tube can be used here.

[2] We have had to make these collars of 1/4 inch brass drilled with a No. 36 drill.

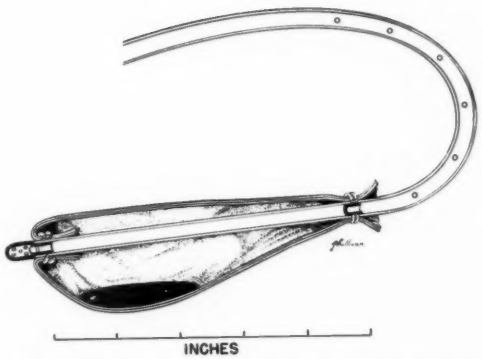

Fig. 1. Diagram of the construction features of the type of Harris tube used by the authors.

ures. A double lumen tube with inflated bag might have been more successful. In the remaining 26 cases, or 87 per cent, the Harris tube worked quite satisfactorily with only minor mishaps; some of these we have encountered before with the Miller-Abbott tube, and others we have learned to prevent.

SUMMARY OF CASES

Type of case	No. of cases	No. of cases requiring over 13 hrs. for passage of pylorus	Complications	No. of cases requiring manipulation under fluoroscope
Paralytic ileus	7	1 case, 24 hours. 2 cases failed	Cases 1, 2, 3	2 without success 1 tip placed at pylorus
Preoperative intubation for bowel resection	12	0	Cases 4, 5, 6	0
Small bowel obstruction	7	1 case, 24 hours. 1 case failed	Cases 7, 8	1 tip placed at pylorus
Volvulus	2	0	Case 9	0
Malfunctioning enterostomy	2	0	0	0

The following case reports are presented to show some of the difficulties and complications we have encountered in the use of the Harris tube.

CASE 1. M. C. 538229. This 50 year old woman entered the hospital with an irreducible procidentia of 2 weeks' duration. The mass was the size of a football and consisted of a protruding everted vagina containing bladder, bowel, and uterus. We were unable to correct the prolapse manually even with the patient in Trendelenburg position. Examination also showed a carcinoma of the left breast with axillary metastases, an anemia of 6 grams per cent hemoglobin, and a tensely distended abdomen with shifting dullness and some high pitched peristalsis. X-ray examination showed a gas pattern consistent with paralytic ileus. A Harris tube was passed with ease, and the procidentia was reduced and strapped in place. Peritoneoscopy established the diagnosis of metastatic carcinoma, and 5,000 cubic centimeters of ascitic fluid were removed. Despite repeated attempts in the course of 48 hours, the Harris tube could not be withdrawn. X-ray film showed the tube to have reached the distal ileum with no kinks or knots. The tube was therefore allowed to pass completely into the gastrointestinal tract and 10 days later was withdrawn by rectal examination in a double bow knot.

Fig. 2. Photograph demonstrating the redundant folds of the bag collapsed about the traversing tube and the pooled mercury. We feel that the ease with which the tube passes the pylorus is closely related to how well the air is evacuated from the bag in the process of constructing the tube.

CASE 2. L. C. 539927. This 60 year old man entered the emergency ward with paralytic ileus and vomiting which he had had for 7 days. A Harris tube was introduced, but several attempts at manipulation under the fluoroscope over a 72 hour period were ineffectual in passing the tube through the pylorus. The patient improved on chemotherapy and was found on x-ray examination to have a cicatrized duodenal ulcer, and later at laparotomy to have a

localized subhepatic abscess exerting extrinsic pressure on the stomach. These combined mechanical factors are considered sufficient explanation for failure of the tube to pass through the pylorus.

CASE 3. I. B. 539297. This 78 year old man entered the hospital with paralytic ileus and vomiting. A Harris tube was introduced but failed to pass through the pylorus despite three manipulations under the fluoroscope. The patient lost ground steadily and expired on the tenth hospital day. Postmortem examination revealed three abscesses in the peritoneal cavity and an extensive carcinomatosis originating in a large gastric lesion which mechanically obstructed the pylorus.

CASE 4. R. deS. 353095. This 73 year old woman had a large carcinoma of the hepatic flexure. A Miller-Abbott tube was started but would not pass the pylorus even after manipulation under the fluoroscope and after the addition of 2 cubic centimeters of mercury into the balloon. A Harris tube made of soft rubber tubing was then used, which under the fluoroscope was seen to go through the pylorus immediately.

This tube descended 8 feet during the 24 hours that elapsed between its insertion and the time of operation. The patient died suddenly during the induction of anesthesia, and the tube could not be withdrawn post mortem.

CASE 5. A. P. 240258. This 48 year old woman was suffering from a carcinoma of the rectum and had a Harris tube passed preoperatively. After 12 hours the tube had made no progress and she was taken to be fluoroscoped. The tip of the tube was found to be in the third portion of the duodenum and the mercury scattered in the small bowel. After removal of the tube the single thickness bag was found ruptured. A new Harris tube with a double thickness bag was used without complications. The free mercury came out of the colostomy 8 days after operation. The patient apparently suffered no ill effects.

CASE 6. A. B. 539900. This was a 65 year old man who had been intubated with a Harris tube for decompression prior to resection of a sigmoid flexure neoplasm. On the seventh postoperative day the tube was removed; and when withdrawn to the cardia, the single thickness bag ruptured allowing mercury to escape into the stomach. The patient suffered no untoward effects.

CASE 7. F. S. 547760. This 24 year old man was intubated with a Harris tube for small bowel decompression. He had had a strangulated inguinal hernia with small bowel obstruction for 4 days. Peripheral circulatory collapse dictated his being placed on shock blocks. Shortly before death, 48 hours after admission and small bowel resection, the end of the tube which had previously passed through the pylorus was found to have been regurgitated back into the esophagus. He had been afflicted with the hiccoughs and the effects of gravity with hiccoughing are considered to have been responsible for the final position of the tube.

CASE 8. E. D. 488067. This 17 year old girl had had an appendectomy and two subsequent laparotomies for acute small bowel obstruction during the 24 months prior to admission. She had been hospitalized by the dental service for an alveolar abscess and again developed acute small bowel obstruction, this time while in the hospital. A Harris tube was passed but was withdrawn 3 hours later in the operating room prior to ascertaining whether it had passed the pylorus. This case is included with those that failed to pass the pylorus.

CASE 9. C. M. 542680. This 59 year old man who had volvulus and strangulation of his small bowel was decompressed satisfactorily for 48 hours following the passage of a Harris tube. On the morning of the third day, the tip of the tube was found to lie in the nasopharynx. It was not clear whether hiccoughing, with which the patient was afflicted, or his own attempt at removing the tube was responsible for this complication.

SUMMARY

An analysis of 30 cases in which a tube similar to the Harris tube has been employed is presented. In 87 per cent of these cases this tube functioned adequately. We feel that the Harris tube is a real addition to the physician's armamentarium. Its advantages are:

1. A rapid and spontaneous passage through the pylorus in a high percentage of cases.

2. A larger suction lumen allowing freer drainage than a double-lumen tube.

3. A single lumen through which the attending nurse may irrigate the tube without the danger associated with irrigating the wrong orifice of a double lumen tube.

4. A smaller total diameter and hence a lesser discomfort to the patient than with a double lumen tube.

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DIVERTICULA OF THE DUODENUM AND JEJUNUM

With a Report of a New Technical Procedure to Facilitate their Removal and a Discussion of their Surgical Significance

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THE purpose of this paper shall be the discussion of known facts concerning duodenal and jejunal diverticula which have appeared in the literature. From this study of the literature and from our own experience we hope to evaluate the surgical significance of these diverticula. Thirdly, we wish to discuss the technical features involved in operations for these lesions and report a new technical procedure which insures against overlooking any duodenal diverticulum at the operating table.

Important reports in the literary history of this subject are few before the advent of roentgenography. Most authors credit Chomel in 1710 with the first description of a duodenal diverticulum. In 1761 Morgagni described a duodenal diverticulum encountered at necropsy. This is relatively recent considering the long ages over which numerous individuals must have suffered from this sporadic lesion and it can be explained only by the fact that diverticula of the duodenum rarely are the direct cause of death. Until Case in 1913 first made the diagnosis in the living individual by roentgenography, practically all of the papers on this subject reported postmortem findings and viewed the clinical aspects only in retrospect. Sir Astley Paston Cooper is credited with being the first to describe jejunal diverticula encountered at autopsy (Ian Fraser). Sir William Osler (1881) also wrote on this subject and described a man, aged 65 years, who died of another cause but who at autopsy showed numerous (53) diverticula of the jejunum. For a long period of time, after his meals he had had crampy pains and loud borborygmi which Osler attributed to filling and emptying of the diverticula.[1] Case, in 1913, had diagnosed 4 cases of duodenal diverticula by fluoroscopic examination and demonstrated his findings in an exhibit at a meeting of the American Medical Association. He described the method used for ascertaining the presence of these duodenal defects in an article published in 1920. Forssell and Key in 1915 first removed a duodenal diverticulum surgically which had been diagnosed preoperatively by fluoroscopic examination. This was the first case in which a direct premeditated surgical attack had been made with the intention of removing a duodenal diverticulum known to be there prior to the operation. This was a very important landmark in the history of this subject, and most papers refer to it as such.

In spite of the fact that duodenal diverticula are not rare, surgical operations to remove or correct these defects are certainly not common. Most of the literature, even of the present day, consists of reports of 1 or 2 cases treated surgically. Articles dealing with operations for 3 and 4 cases are rare and in no instance have we encountered the report of over 4 cases in which operation was successfully carried out. The existing attitude concerning the surgical significance of duodenal diverticula is shown in numerous articles. For example Costello (1933) reported 6 cases, 5 of which definitely gave symptoms but only 1 patient was operated upon in order to relieve the symptoms; and Morton (1940) reported from the University of Rochester that primary duodenal diverticula had been diagnosed in 33 different patients but only 2 were operated upon and in only 1 of the 2 was the diverticulum successfully removed. In 19 duodenal di-

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[1]Although Osler was still at McGill University at the time that this paper was published, his literary style, which developed so beautifully in his later career, already was evident in this report.

verticula diagnosed by roentgenographic examination by Larimore and Graham only 3 patients were operated upon; 2 of these operations failed to reveal the diverticulum, but postoperative roentgenograms showed that it was still present and that it had been missed at operation. This low incidence of operation is revealed throughout the literature in spite of the fact that presumably the gastrointestinal roentgenographic study has been made because of the presence of symptoms. Certainly the explanation for the failure to operate in the presence of positive lesions encountered and proved by roentgenographic study must be due either to the relief of symptoms by medical management or a recognition of a concomittant lesion which explains the symptoms, and for which surgery is done or medical management succeeds in relieving. Otherwise the low incidence of surgery for these proved lesions originates from an indifference as to their presence and an existing feeling that surgery cannot safely relieve the symptoms. Medical management apparently does not relieve well established symptoms resulting from duodenal diverticula. The medical management consists of diet, mineral oil and posture, lying down laterally after each meal, a painless but probably not such an easy measure to carry out since it must be continued indefinitely. Coexisting lesions such as cholecystitis, peptic ulcer, etc., which could give similar symptoms, are not found in a sufficiently high percentage of the cases of duodenal diverticula to explain the failure to remove the diverticulum in a great number of patients. In the literature, instances are recorded in which there are actually associated lesions such as cholecystitis; cholecystectomy would be performed with no effort made to remove the diverticulum. This fact shows again the real reason for the low instance of operations in series of reported cases of duodenal diverticulum, namely the indifference as to the presence of the diverticulum and failure to appreciate that it can and does cause severe and constantly annoying symptoms which in good surgical hands can be relieved. Undoubtedly there is an existing temerity about the operations on the duodenum both in the minds of clinicians and also to a lesser extent in the minds of surgeons mainly for fear of duodenal fistula which admittedly would be a horrible complication for an elective operation.

A study of the literature reveals how frequently surgeons operating for a duodenal diverticulum have failed to locate and remove it. This failure is well demonstrated in several articles. Robineau and Gally reported 5 operations for duodenal diverticula; in 4 of them the diverticulum was missed and left. Downes also reports failure to find the diverticulum at operation in 1 of 4 cases. In our first case we missed 2 out of 5 diverticula of the duodenum existing in 1 patient. The 2 diverticula were disclosed roentgenographically after operation (Fig. 1). They apparently were covered by pancreatic parenchyma and probably did not cause symptoms, for the patient was relieved of her gastrointestinal complaints. This failure caused us some chagrin and since then we have used a method which makes the disclosure of the duodenal diverticula almost a certainty so that by careful surgery they may be exposed and removed.

INCIDENCE

It may be surprising that duodenal diverticula are disclosed roentgenographically in some series of cases as frequently as Meckel's diverticula are found at necropsy. Necropsy studies show a relatively high percentage of duodenal diverticula. Baldwin reports finding diverticula in 15 out of 105 dissections, an instance of 14.5 per cent. Undoubtedly many of these diverticula were small but this high incidence at least shows the tendency to the formation of diverticula in the duodenum.

Beals has found 41 duodenal diverticula in 1,887 roentgenographic examinations (2.2%). Larson found 36 duodenal diverticula in 2,250 roentgenographic examinations (1.6%). Bristow at the Baptist Hospital in New Orleans in 1,700 gastrointestinal roentgenographic studies from January 1946 to March 1947 found duodenal diverticula in 20 patients, an incidence of 1.2 per cent. Undoubtedly the care and detail with which roentgenographic studies are made affect the incidence of disclosure of duodenal diverticula. One series of x-ray studies of which we have seen reports gives an incidence of 0.5 per cent. It is true that some of these diverticula are relatively small and

some of them are huge; but residual pooling of barium in the diverticulum is apparently a common finding and in our opinion should be an important distinguishing feature in judging whether operation for the diverticulum would actually relieve the symptoms. Roentgenographic studies to be thorough must include recumbent and lateral positions and pressure filling of the duodenum and in addition a serial roentgenogram taken in 6 hours to determine residual pooling in the diverticulum.

SEX

Studies found in the literature do not clearly distinguish a predilection of either sex to form these diverticula. Hahn collected 207 cases from the literature and estimated that 54 per cent were in women and 46 per cent in men. Spriggs and Marxer reported of 38 cases disclosed roentgenographically 20 were women and 18 were men. In 85 cases discovered roentgenographically, Case found 60 per cent in women, 40 per cent in men; whereas the sex distribution of 55 cases reported by Centano, was 15 women (33%) and 37 men (67%). Apparently the distribution is almost equal in the two sexes.

LOCATION

Most of the duodenal diverticula occur on the concave side of the descending portion. The majority of them occur in the region of the ampulla of Vater and for that reason they have been called "perivaterian" diverticula by the French. When they occur on the second portion of the duodenum they either present into the head of the pancreas and are covered by it or, more commonly, originating in the perivaterian area, they lie posterior to the duodenum with a fundus extending even to the right of the duodenum giving the impression on roentgenographic study that they may be attached to the right border of the duodenum. Such apparently rarely, if ever, occurs. Diverticula of the second portion of the duodenum rarely ever protrude anterior to the head of the pancreas. There apparently are exceptions to this (Wilkie, Baldwin). Next to the perivaterian area the concave inferior transverse portion of the duodenum is the site most often affected. The diverticula here present upward and are covered by the transverse mesocolon and are associated with the ligament of Treitz. Diverticula apparently do not occur on the inferior border of the third and fourth portions of the duodenum. Diverticula occur even less frequently in the first portion of the duodenum. They are apparently rare there except as "pseudo" diverticula caused by pouching due to contracture of an ulcer. However, genuine diverticula do occur in the first portion of the duodenum and apparently from roentgenographic pictures presented in the literature they occur on the superior border more often than on the inferior. The following statistics bear out these statements. In roentgenographic studies of 5,263 cases reported by Centano, 55 patients showed duodenal diverticula. In 37 of the patients (67%) a diverticulum was found in the second portion of the duodenum. In 17 patients the diverticulum was situated in the third or fourth portion. All of the 15 diverticula discovered by Baldwin at necropsy were on the concave descending portion of the duodenum. The diverticula are more commonly found single but two or more may exist. In 70 per cent of those cases reported by Nagel the diverticulum found in the duodenum at necropsy was a single diverticulum. In 30 per cent of the instances 2 or more were found. Spriggs and Marxer reported that 84 per cent were single and 16 per cent were multiple. This was a roentgenographic study. In Baldwin's series of 15 necropsy cases 2 (14%) showed multiple diverticula. In 1 of our cases 3 diverticula were found at operation, 2 additional in the same case were missed. Multiplicity is an extremely important feature of course to the surgeon. He can expect to find more than 1 diverticulum in a sufficiently high percentage of cases to be always wary of missing others even after one has been disclosed and removed.

PATHOLOGY AND ETIOLOGY

Much of the older literature on this subject is concerned with the pathology and causes of duodenal diverticula. Indeed it would seem that the papers of least practical importance devote themselves largely to such a discussion. Various definitions and terms are associated

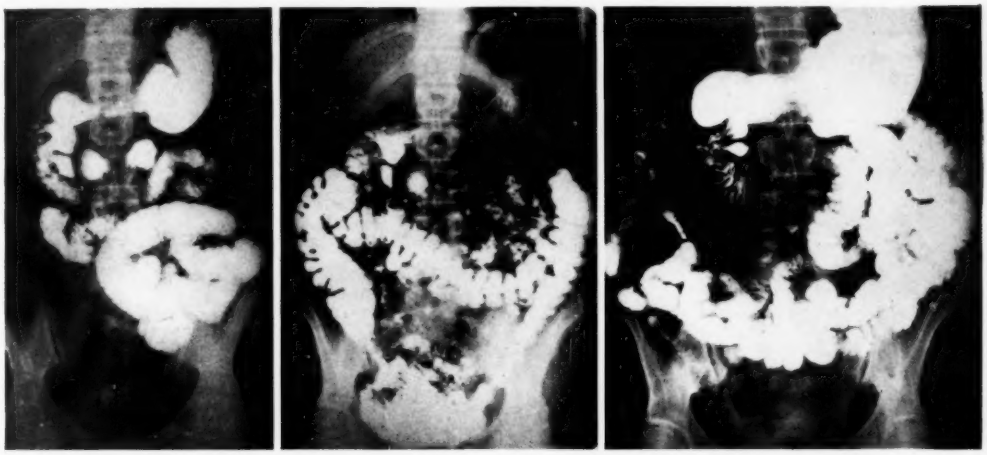
with these diverticula but now that the real importance, that is the diagnosis and relief of symptoms caused by these conditions, has become a realization, these repetitious discussions seem highly pedantic. We, however, like other authors before us are tempted to repeat these definitions. Diverticula are generally divided into true and false; true meaning those in which the wall of the diverticulum has all the layers of the duodenal wall; false diverticula are those in which the muscularis is absent from the walls and in which there is a herniation of the mucosa through a defect in the muscularis making the diverticula walls consist only of mucosa and serosa or mucosa alone. In addition to this, diverticula are divided into genuine and pseudo, pseudo diverticula being relative pockets on the duodenum caused usually by contraction of an ulcer scar, and genuine diverticula being out pouchings of a true or false nature beyond the usual limits of the duodenal confines. Also diverticula are sometimes divided into congenital and acquired which distinction is most hard to define since congenital diverticula existing soon after birth are extremely rare.

The diverticula themselves by far the majority of which are herniations of the mucosa or false diverticula are extremely delicate and thin walled, soft and compressible. Usually the os of a diverticulum is quite large and obstruction of it is rare, but the os is fixed by virtue of the fixation of the duodenum, and for that reason when a large diverticulum fills and the patient remains in the erect position retention of the contents may continue for hours. Emptying and filling of jejunal diverticula on the other hand must occur with equal facility. The jejunum being relatively unfixed in position undoubtedly swings and churns and changes position sufficiently often to prevent prolonged retention. This accounts for 2 important facts, first a jejunal diverticulum more rarely gives symptoms than duodenal, and jejunal diverticula are rarely disclosed on roentgenographic examination, mainly because retention is absent.

ETIOLOGY

The causes of duodenal diverticula are not well understood. The condition is seldom seen early in life; it usually occurs in the fifth, sixth, or seventh decade. Various authors have discussed the etiology and among the theories which have been mentioned are herniation of the mucous membrane through a place of lowered resistance in the duodenal wall. This place of lowered resistance, it has been alleged most frequently, is due to the penetration of small vessels through the muscular layer. A less often mentioned possible cause of weakness of the wall is the presence of pancreatic tissue at such an area or the presence of fat in the muscularis. Another often expressed theory regarding the formation of these diverticula is that they are caused by outpouching of the duodenal wall similar to the anlage from which developed the liver and the pancreas. Other causes which have been cited are traction either of the pancreatic or common duct or from the head of the pancreas itself when it has undergone focal or widespread atrophic changes due to chronic interstitial pancreatic disturbances. These theories seem to us less tenable than the theory that herniation occurs at a weak spot caused by penetration of the vessels. To substantiate the latter idea is the fact that practically all the diverticula occur on the side of the duodenum or jejunum where the arteries enter and seemingly never on the other border. In the 2 cases we report herein the jejunal diverticula which were large and numerous (Fig. 2) were on the mesenteric side and in reality were outpouchings of the mucous membrane between the serosal coverings of the mesentery. The diverticula in this instance were alternately a little to one side and then the other of the line of attachment of the mesentery. Careful examination of jejunal mesenteric attachments demonstrate that the vessels alternate irregularly first on one side and then on the other of the central line of attachment to the mesentery.

Diverticula of the first portion of the duodenum may occur on the superior arch of the duodenum. In the 1 case which we have seen of the diverticulum of the first portion of the duodenum the diverticulum was a true diverticulum whose walls consisted of all coats of the intestine (Fig. 3). It is probable that genuine diverticula in this area while more rare



a b c

Fig. 1. Roentgenograms showing duodenal diverticula (Case 1). a and b, Preoperative roentgenograms show 2 large cascade diverticula of the third portion of the duodenum. At operation these proved to be the right and left of the superior mesenteric vessels. They were excised. There are also 2 diverticula in the descending portion of the duodenum. A retroduodenal diverticulum was inverted at operation. c, Postoperative roentgenogram shows that 2 diverticula in the descending portion of the duodenum persist and were missed at operation. These were probably in the pancreatic parenchyma. At the time that this operation was carried out we were not using air insufflation of the duodenum in order to disclose the location of the diverticula present.

than in the second and third and fourth portions of the duodenum are always true diverticula and they are congenital in origin. They possibly represent the anlage of "pyloric coeca" —pouches which occur in certain species of fish, and which empty into the duodenum (Kyle). Perhaps this explains why all genuine diverticula in this position are true diverticula. In this presentation we absolutely exclude any consideration of pseudo diverticula caused by scarring of an ulcer.

SYMPTOMATOLOGY

There are no characteristic symptoms of duodenal diverticula to substantiate, with any degree of certainty, a presumptive diagnosis of such a condition. Undoubtedly many of the diverticula of the duodenum remain asymptomatic. If one were to base the percentage on autopsy findings probably duodenal diverticula would be asymptomatic in 85 to 90 per cent of cases. However, in a series of duodenal diverticula diagnosed roentgenographically, probably the incidence of asymptomatic ones is only 25 per cent. This rough guess is based on surmises from reports in the literature and has not been substantiated by actual clinical count. Five of 6 diverticula reported by Costello were responsible for symptoms. Spriggs and Marxer estimate that in 47 per cent of their cases the diverticula were responsible for the symptoms.

The most common symptom produced by these lesions is pain. This apparently occurs in about 80 to 85 per cent of the symptomatic cases. The pain is usually dull; it is mild to extremely severe. It may be a mere discomfort or an excruciating agony. It may last minutes to several hours. It occurs in the right subcostal region but much lower than gall-bladder pain. In reality it is located in the right lower portion of the epigastric region away from the costal region and just above and to the right of the umbilicus. This pain may radiate through to the back or at times rarely to the right scapula. It is questionable whether the pain of duodenal diverticulum itself ever radiates to the scapula, since in cases in which this has been noted cholecystitis was an associated finding. The time of occurrence of pain is irregular. It apparently is associated with meals but not in a definite time pattern. Experience questioning patients regarding the occurrence of pain after

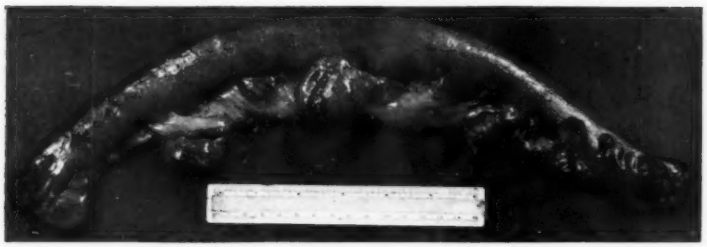


Fig. 2. A segment of the jejunum removed at operation (Case 5). It is 12 inches in length and contains 7 large and many smaller diverticula. These are false diverticula, thin walled, and consist of mucosa covered by peritoneum. As is usually the case these diverticula protrude through fenestra in the muscularis. They are commonly found on the mesenteric side at the site of entrance of the vessels.

meals left us with no definite idea of a pattern. Apparently it may come soon after a meal or hours after a meal. It may occur on consecutive days and then not occur for weeks. Apparently the pain is due to filling and failure of adequate emptying of the diverticulum. In 1 of our patients pain had the periodicity of a peptic ulcer but the patient did have peptic ulcer in addition to the large diverticulum. Associated with this pain objectively is tenderness. In 1 of our patients in whom pain was a very pronounced symptom the tenderness was striking in the right lower portion of the epigastric region and this was consistent. In the presence of pain there was always tenderness. There was no tenderness directly under the subcostal margin. The second symptom of importance and frequency in these patients is nausea. This is often recorded in the case reports in the literature. In 1 of our patients this alone was the presenting symptom. The patient stated that she has been nauseated for some 12 years. The time of occurrence of nausea was irregular but it had become more frequent in time and duration so that in recent years it occurred daily. She had sought medical aid on numerous occasions and from various physicians but until we studied her the results of examinations had been negative so that the diagnoses previously made had varied between functional gastrointestinal disturbance and neurasthenia. The nausea may be very severe. It may be accompanied by vomiting, but this is rare. Nausea may occur at the height of pain but it may occur separately and without pain. This is understood better if one subscribes to the very probable theory that nausea in reality originates in the duodenum, and not in the stomach. Distension of the duodenum or diverticulum of the duodenum is the cause of nausea though the full diverticulum resting on the duodenum may cause partial obstruction and in that manner produce nausea. The third symptom of importance is diarrhea. This occurs far more commonly than one would expect. It is noted frequently in the case reports in the literature. It was a prominent feature in 1 of our patients. Apparently the diarrhea is caused by a pancreatic disturbance. It consists of 4 to 6 loose stools a day extending over a period of a few days. One author (Fulde) has written on chronic disturbance of the pancreas due to duodenal diverticula. In his cases in which he described disturbed pancreatic function, diarrhea and a high fat content in the stools were prominent features. Apparently the pancreatic duct may be obstructed partially without obstruction of the common bile duct. Both acute hemorrhagic pancreatitis and jaundice have been described as resulting from duodenal diverticula but that degree of severity of pancreatic disturbance is very rare.

Various other symptoms have been mentioned in the case reports of duodenal diverticula including pain in the posterior lumbar region, sensation of fullness after eating, symptoms simulating cholelithiasis and those simulating peptic ulcer of the duodenum. Weight loss is an imposing feature of certain case reports, the patients having lost 20 to 30 pounds.

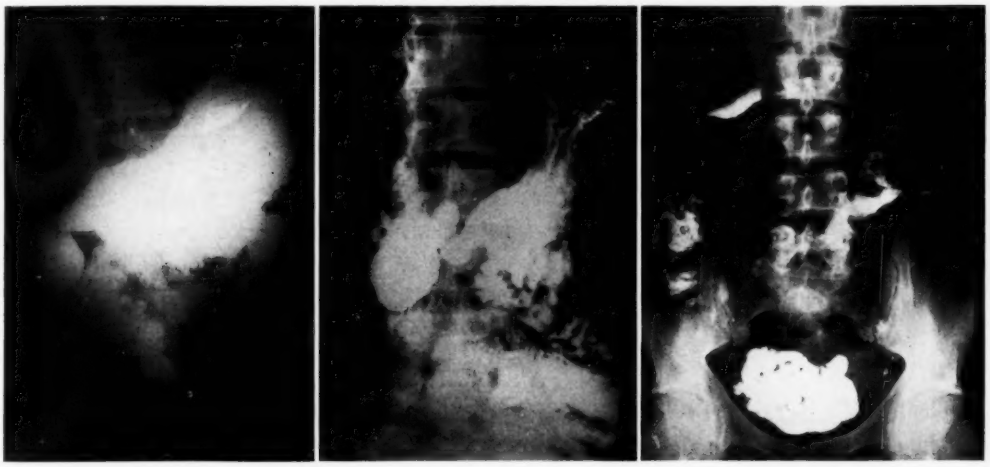


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Fig. 3. Roentgenograms showing a huge diverticulum of the first portion of the duodenum in a young man exhibiting symptoms simulating peptic ulcer (Case 4). This is a genuine, true diverticulum, and one whose walls are made up of all the coats of the duodenum. This may be equivalent to the pyloric cecum of fish. In this case a gastrectomy was done. a and b, The preoperative roentgenographic appearance of the diverticulum immediately after the ingestion of barium. c, Residual pooling of barium in the diverticulum 6 hours after the ingestion of barium.

The symptoms of duodenal diverticula may continue and usually do over a period of many years without the diagnosis being made. Indeed the diagnosis is rarely suspected merely from the subjective complaints of the patient because whatever symptoms a duodenal diverticulum causes may be attributable to the other conditions.

COMPLICATIONS

Complications of duodenal diverticula are not common but the most bizarre complications do occur. Acute diverticulitis has been reported with the severe symptoms of an acute abdomen. Recovery of patients following surgical removal of acutely perforated duodenal diverticula has been reported by Huddy, Lucinian, Monsarrat. Acute perforation results in the symptoms of severe acute abdominal catastrophe. Boland (1936) has done the profession a service to call attention to the fact that an acutely inflamed diverticulum which has caused peritonitis can be overlooked unless the surgeon is cognizant of this possibility. He operated upon a patient and it was recognized that the man had peritonitis but no definite origin of the condition could be ascertained at operation. The patient died and at necropsy an acutely perforated duodenal diverticulum was found to explain the process. If the knowledge of this possibility is realized by the surgeon when there is an otherwise undisclosed cause of peritonitis the surgeon will not fail to seek this explanation and thus possibly save his patient. Beaver reported a similar case. Melchior described phlegmonous duodenitis resulting from diverticulitis. Hemorrhage is another rare but apparently authentic complication of diverticula of the duodenum.

Obstructive jaundice is another complication which though rare may be due to either pressure by the diverticulum or to an enterolith in the diverticulum as in the case reported by Nicholson. Harris and Watson and Terry and Mugler have reported stones in diverticula. Another complication which seems to be extremely rare is carcinoma occurring in the diverticulum. Strode has reported 1 such case. The patient operated upon with removal of duodenum and head of pancreas and recovered.

DIAGNOSIS

There are two ways in which the diagnosis may be made. It may be confirmed after it is

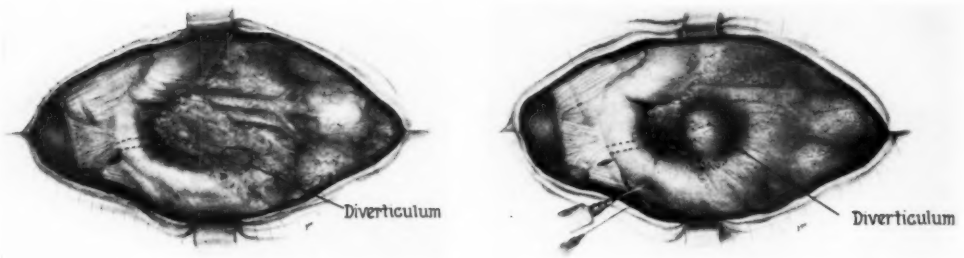

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Fig. 4. Representation of a diverticulum of the descending portion of the duodenum protruding into the pancreas. a, Before, and, b, after insufflation of the duodenum with air. After the duodenum is pumped up with air the head of the pancreas bulges disclosing the position of the diverticulum. Diverticula of the descending portion of duodenum have often been missed at operation. This is an added technical help in disclosing their position at operation.

suspected by a very astute clinician who has various investigations made such as cholecystograms and a roentgenographic search for duodenal ulcers with instructions to the roentgenologist to make a careful examination for duodenal diverticulum; or the diagnosis may be stumbled upon without its possibility having been considered by the clinician and with it becoming manifest only, as it were, accidentally during a gastrointestinal roentgenographic study which was made with the thought that peptic ulcer may be causing the symptoms. Obviously it is more gratifying to have considered the correct diagnosis and have it disclosed by roentgenography. Instructions to the roentgenologist that duodenal diverticulum is a possibility will undoubtedly result in disclosure of this lesson in a higher percentage of cases.

The diagnosis of duodenal diverticulum is not easy even though the diverticulum be sufficiently large to cause the symptoms for which the patient sought relief. Almost any type of upper gastrointestinal complaint from mild to severe may be attributable to duodenal diverticulum. The thought of this possibility makes the diagnosis easier. Subjectively there is nothing characteristic about the symptoms to lead one to the correct diagnosis and even a presumptive diagnosis is not justified on subjective evidence. Objectively tenderness in the right lower portion of the epigastrium is a suggestive but not a conclusive finding. The real diagnosis of duodenal diverticulum depends upon its roentgenographic exposure. Then and only then is one justified in making the diagnosis with any degree of assurance. When the diagnosis has been made there is still the problem of evaluating the relationship of the diverticulum to the symptoms. The mere fact that a diverticulum is proved to be present in a duodenum does not assure one that it alone is responsible for symptoms. For that reason whenever this diagnosis is being established it is important to have a cholecystogram and roentgenographic studies of the gastrointestinal tract. Then careful consideration of the subjective and objective findings in the case may lead one to a true evaluation of the part a duodenal diverticulum is playing. Residual pooling of the barium in the diverticulum would seem to be a very important feature upon which to base judgment as to whether the symptoms are largely due to the diverticulum itself.

JEJUNAL DIVERTICULA

Diverticula are found in the jejunum more rarely than in any part of the gastrointestinal tract. Fraser indicated the frequency of diverticula in the various parts of the gastrointestinal tract as follows; first colon, second ileum (Meckel's diverticulum), third duodenum, fourth pharynx and esophagus, fifth stomach, sixth jejunum. When diverticula occur in the jejunum they are most frequent near the ligament of Treitz and diminish distally in size and number. They are most often multiple and are found in numbers from a few to hundreds in any given cases. They practi-

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Fig. 5. Diverticulum of the descending portion of the duodenum which has presented posterior to the duodenum before and after mobilization of the duodenum. Diverticula of the descending portion usually occur around the ampulla of Vater and usually the fundus is located posteriorly to the duodenum itself, necessitating an incision in the peritoneum lateral to the duodenum on the right with elevation of the duodenum and the pancreatic head. b, The duodenum here is represented as being turned to the left. A hemostat is placed across the base of the diverticulum prior to its excision. The fenestrum in the muscularis is then closed with interrupted silk stitches.

cally always occur as false diverticula, that is as herniations of the mucous membrane through the muscular coat of the intestinal wall. The diverticula protrude through fenestra between the leaves of the attachment of the mesentery at the point of emergence of arteries. They may be huge. One as large as an apple and 6 as large as billiard balls were reported in 1 case by William Osler.

The extreme infrequency of these lesions is illustrated by such facts as those reported by Rosedale, viz., 3 instances of diverticulosis of the jejunum in 5,000 autopsies; and Edwards 9 cases of diverticula of the jejunum in 2,820 autopsies, an incidence of 0.3 per cent. Radiographic disclosure of jejunal diverticula during life is even more rare. Rankin reported that in 72,715 gastrointestinal examinations of the stomach and duodenum, 111 duodenal diverticula were found (0.15%) and in 956 stasis or serial x-ray examinations of the small bowel only 3 instances of jejunal diverticula were found. The cases of diverticula of the jejunum and ileum at the Mayo Clinic up to 1932, total 52; 3 found roentgenographically, 18 discovered at operation, and 31 at necropsy. These did not include Meckel's diverticulum nor diverticula of the duodenum. Thirty-eight were males. Thirty had symptoms relative to the gastrointestinal tract. Forty-one had diverticula of the jejunum, 13 of the ileum. At no time did a patient go to surgery for relief of symptoms thought to be due to the diverticulum.

Jejunal diverticula cause symptoms in a much smaller percentage of cases than duodenal diverticula of comparable size. The reason being that the duodenum is fixed and the jejunum relatively free and motile constantly changes the position of the ostia of the diverticula so that emptying is facilitated. Pain, borborygmi, and flatulency have been cited by numerous authors as the usual symptoms of jejunal diverticula. William Osler described a case in which a patient avoided his companions immediately after meals because of the loud noises which resulted from filling and emptying of the diverticula. Pain may be very severe and crampy. Diverticulitis of jejunal diverticula though rare has been reported by Ovens and others. Actual perforation also occurs according to Shutkin. Enteroliths occurring in a jejunal diverticulum may cause obstruction as reported by Watson, and Terry and Mugler. Obstruction resulting from adhesions to jejunal diverticula has been reported by Hubeny and Pollack.

Apparently in the past, even when the gastrointestinal symptoms are present, surgeons and clinicians have been unwilling to attribute them to diverticula of the jejunum disclosed either at operation or by roentgenographic examination. Perhaps this incredulity has been partially due to a sensation of danger attached to the removal of these diverticula or to resection of the jejunum. Now that surgery of this part of the alimentary tract has been made relatively safe by numerous advances in re-

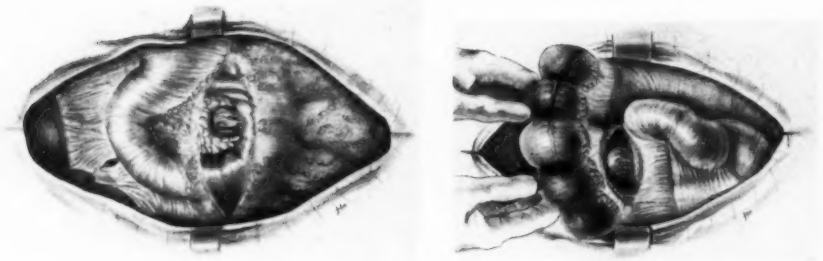

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Fig. 6. Diverticula of the third portion of the duodenum usually arise from the superior concave surface. These may be approached through the transverse mesocolon by an incision into its superior layer, a, or if they are further to the left of the superior mesenteric vessels they may be approached through the transverse mesocolon from below as represented in b. These diverticula may be easily excised or inverted and the fenestrum in the muscular layer closed with interrupted silk stitches. The peritoneum is carefully closed over this.

cent years, the indications for direct attack on these lesions must be broadened and undoubtedly when more such lesions are commonly alleviated by capable surgeons who then report their good results, it will be more readily accepted that prompt removal of them is indicated when they produce troublesome symptoms.

TREATMENT

The treatment of diverticula of the duodenum and jejunum depends on whether they are causing symptoms or not. Presumably their disclosure by roentgenographic examination is always in a patient who has some gastrointestinal symptoms. Even when diverticula are known to be present, it sometimes, though not usually, may be justifiably concluded, that they are not the cause of the patient's symptoms. For example cholelithiasis may also have been demonstrated when the symptomatology is typical of cholecystitis and cholelithiasis. In such instances judgment as to whether the diverticulum should be removed is secondary to judgment on the indications for treatment for cholelithiasis. Usually both lesions should be removed simultaneously.

When it is concluded that the diverticula are causing symptoms the question of treatment cannot be divided into medical or surgical. It can only be decided on the basis of whether surgery can justifiably be denied the patient because of the gravity of his symptoms; or justifiably offered him because of the minor nature of his complaints. In reality there is little medical treatment. Among measures which have been suggested are bland diet, mineral oil, and lateral recumbency on one side or another after each meal. Acceptance of this management is justified only for patients whose physical condition precludes operation. Otherwise surgery is indicated if the symptoms are severe enough. Complete relief by surgery can be expected with an extremely low risk to the patient. In the past too little appreciation and experience with the effects of these diverticula have left surgeon and clinician without appraisal of the results of surgery. For that reason clinicians have hesitated to recommend removal by the surgeon and the surgeon perhaps himself did not realize what tremendous relief he could give his patient by removing the diverticula. Perhaps the fact that today the risk has been greatly diminished over that of even 10 years ago justified a more radical attitude toward these lesions either when they are disclosed by roentgenographic examination or found incidentally at the operating table.

TECHNICAL FEATURES OF THE OPERATION

Removal of the diverticulum appeals to us as the most desirable operation provided other factors permit this to be done without unjustifiably increasing the risk to the patient. Location of the diverticulum at operation is not al-

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Fig. 7. Roentgenograms showing a diverticulum of the descending portion of the duodenum arising near the ampulla of Vater (Case 2). In a the position of the diverticulum has been indicated by surrounding it with white lines. The diverticulum is partially filled. b, Six hours after ingestion of the barium meal the diverticulum still retains part of the barium. This patient had severe attacks of pain preoperatively. She has been completely relieved of all symptoms for a period now of 18 months following the operation. c, Postoperative roentgenogram disclosing no evidence of the diverticulum which was excised at operation.

ways easily accomplished. As has been indicated above, these diverticula have been missed in a high percentage of the patients operated upon and even by extremely able surgeons. The diverticulum itself extending posteriorly may be entirely covered by the duodenum or protrude to the right of the duodenum. Others occur in the head of the pancreas and when collapsed in the prepared patient who has been fasting and at the operating table they may not show. For this reason we have devised the following means of demonstrating the position of the diverticulum. A 20 cubic centimeter syringe carrying a 22 gauge needle is used. The needle is inserted into the duodenum and the duodenum is pumped up with air. Thirty to 40 cubic centimeters of air is necessary. When the duodenum is ballooned out the diverticula may be disclosed even if they are in the head of the pancreas and entirely covered by parenchyma (Fig. 4). Under the circumstance of air insufflation the head of the pancreas expands, so that a diverticulum therein may be discovered. This also shows diverticula in the third and fourth portions of the duodenum in the leaves of the transverse mesocolon. After the lateral peritoneal attachment of the duodenum is severed and the duodenum is turned partially forward any posterior diverticulum may be disclosed (Fig. 5). The diverticulum is then carefully dissected from surrounding structures and the neck severed between two clamps. The edges of the mucosa which have been agglutinated by the pressure of the clamp are inverted using chromic No. 00 catgut suture. The muscular defect and the serosal layers are closed with interrupted silk stitches. Diverticula in the region of the ligament of Treitz may be difficult to disclose. We have severed the inferior fold of peritoneum on the transverse mesocolon to approach these (Fig. 6) and by pumping up the duodenum they may be found and excised. Diverticula of the third portion of the duodenum to the right of the mesenteric vessels may be approached through the superior leaf of the transverse mesocolon.

A diverticulum protruding into the head of the pancreas may be very difficult to remove but merely because of position; removal is not impossible. Separation of the pancreatic parenchyma from the diverticulum may be achieved by careful dissection. We did this in

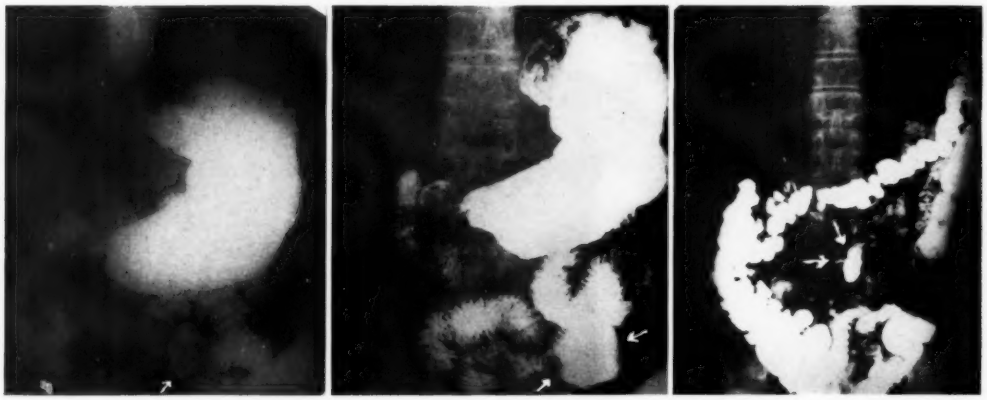

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Fig. 8. Jejunal diverticula shown roentgenographically in various phases. Arrows indicate the position of the defects. In this instance (Case 6) a segment of jejunum containing 2 large and several smaller diverticula was resected.

1 of our cases in which the diverticulum was quite large and in which it was necessary to remove pancreatic parenchyma from the entire sac. The technical feature advocated by Maclean of opening the duodenum and inserting the finger into the diverticulum may facilitate removal of a diverticulum so located. We have not employed this method. Ferguson and Cameron advocated giving the patient a mixture of barium on the evening before or morning of the operation to facilitate disclosure of the lesion at operation. The barium coats the diverticulum and makes it appear white.

Inversion of the diverticulum after the sac is entirely separated from the surrounding structures is easily accomplished. This maneuver is very tempting because it offers a certain amount of security against leakage and contamination, but somehow it is not as appealing as complete removal of the diverticulum. When the diverticulum is closely associated with the common bile duct and when its removal and necessarily tight closure may compromise the patency of the duct or when other technical features would make removal an increased risk, inverting the diverticulum may be the best choice. We have inverted several in our cases some of which we feel today we would remove in preference. Barnes is to be credited with the assertion that inversion may be followed by enlargement of the mucous membrane with the accumulation of a gelatinous material inside the inverted diverticulum and that this ultimately may lead to obstruction. His authority for this is difficult to find, since he does not report this as having occurred in his cases and since he does not quote specifically another author to substantiate the statement. Nevertheless, the larger diverticula if inverted might cause partial obstruction or interference with the intestinal flow. Because of the lack of peritoneal covering on the posterior and pancreatic surfaces of the duodenum the diverticula arising there, if not too large, may be inverted as additional safety to prevent leakage since there is absence of serosal covering. Diverticula of the terminal portion of the duodenum may easily be excised, the mucosa sutured over with catgut and interrupted silk stitches employed to close the muscular and serosal layers.

Diverticula of the first portion of the duodenum may easily be excised even though they are true diverticula. If there is an occasion for excision of a segment of the stomach as there might well be when there is a stenosing ulcer, excision of the diverticulum at the same time is a procedure of choice.

Numerous operations have been advocated and done for duodenal diverticula. It is obvious to most authors that excision is a most desirable procedure but fear of excision has lead many to choose other less effective operations.

Among operations done in the past have been gastroenterostomy, gastroenterostomy with exclusion of the duodenum, excision of the diverticulum, inversion of the diverticulum, dissection of the diverticulum permitting it to remain, enteroenterostomy to short circuit the bowel contents around the jejunal diverticulum, excision of the duodenum and head of the pancreas (for carcinoma in the diverticulum).

Jejunal diverticula are less frequently operated upon. Since they are usually multiple and since their ostia are sometimes exceedingly large, excision of a long segment of jejunum may be the best procedure. Dissection and removal of each diverticulum might entail a very tedious procedure with more element of danger from leaks at numerous places. If there is one large diverticulum, excision is advisable or, if it is extremely large with a wide os, resection of this jejunal segment with anastomosis is indicated.

CASE REPORTS

The following are brief case reports of 6 cases of duodenal and jejunal diverticula. Four of these patients had duodenal diverticula and 3 had jejunal diverticula. All of these patients had symptoms. Five of them had symptoms from the diverticulum and in each instance operation relieved them of these symptoms. The sixth patient had a gastric ulcer and at operation giant diverticula of the jejunum were discovered. It was feared that if the jejunum was anastomosed to the stomach with these giant diverticula opposite the stoma, the fixation thus of the jejunum would result in symptoms of stasis or obstruction. It is possible that these diverticula were already giving symptoms but, if they were, the symptoms were overshadowed by those of the severe gastric ulcer.

CASE 1. E.R.S., a white female, aged 62 years, gave a history of epigastric pain and discomfort for the preceding 2 years. These symptoms were very severe at times, and there was no definite relation to eating. During the year before admission to the hospital her symptoms became worse and she lost 15 pounds in weight. Objectively there were few findings of significance. There was slight tenderness in the epigastrium. Roentgenographic examination with a contrast meal revealed diverticula of the duodenum, 3 of them being quite large (Fig. 1). After observation here she returned to her home in a distant city but the pain became very severe and she decided to return for an operation which had been offered her with the prospect of relief but had not been urged upon her.

At operation the peritoneum was cut on the right lateral border of the duodenum and the duodenum was mobilized and turned toward the left to expose its posterior surface. There a large diverticulum was exposed (Fig. 5). The sac was remarkably thin and consisted only of herniated mucosa. It had the same diameter as the bowel. Near the medial border in the region of the ampulla of Vater was a large oval fenestration in the muscular layer. The os was quite large. The diverticulum was inverted into the lumen of the diverticulum and the margins of the fenestrum approximated with interrupted silk sutures. The third and fourth portions of the duodenum were approached through the inferior surface of the transverse mesocolon. Arising from the superior concave portion of the third part of the duodenum were 2 large diverticula each 3 centimeters in diameter. One was found on each side of the superior mesenteric vessels. Each of these was excised. The mucosa was closed with fine catgut and the fenestra in the muscularis through which these had herniated were closed with interrupted silk stitches.

At this time we were not using air insufflation to disclose diverticula. Postoperative roentgenographic studies revealed that we had missed 2 diverticula of the descending portion of the duodenum (Fig. 1). Apparently the retroduodenal one inverted at operation did not show on preoperative examination. Those which were missed may have protruded into the head of the pancreas. These fortunately were not the largest diverticula and may have been asymptomatic since 1 year after operation this patient reported that she was free of gastrointestinal symptoms. Unfortunately, however, she was left with a tragic residual of the operation. This operation was done soon after the advent of "continuous spinal" anesthesia. Permanent nerve damage to the cauda resulted in bladder residual and slight rectal incontinence.

CASE 2. J.W.T., a white female, aged 27 years, complained of intermittent upper abdominal pain which had been occurring for some 3 years and was increasingly more severe. The pain was always in the same place to the right of the midline and low in the epigastrium or just above and to the right of the umbilicus. A "nauseated feeling" had often been present with or without the presence of the pain. This sensation and the pain were both initiated or increased by eating. It was almost always present in recent months. At times the pain was most severe. It was dull and did not radiate but during some attacks it did require opiates for relief. Objectively the only significant finding in the entire physical examination was definite tenderness in the right lower epigastric region. It was variable in severity but when she had nausea or pain tenderness was always present. Roentgenographic examination

disclosed a large diverticulum arising from the descending portion of the duodenum.

The diverticulum was found at operation arising from the posterior surface at the midportion of the descending segment of the duodenum. In order to approach the diverticulum the duodenum was mobilized and turned to the left. The common bile duct was found to enter the duodenum at the base of the diverticula. The diverticulum was excised, with care not to injure the common duct. The fenestration in the muscular coat was closed with chromic No. 00 catgut and a double row of investing fine silk sutures. The postoperative course was uneventful. Since operation 15 months ago, this patient has had complete relief of her symptoms. Postoperative roentgenographic examination failed to reveal any evidence of the diverticulum (Fig. 8).

CASE 3. H.M.H., a white female, aged 51 years, had constant nausea for the past 12 years. The patient had been treated elsewhere for years with diets but no relief was experienced. This patient had no symptom other than nausea. The nausea was very severe. She said she was always nauseated. Various examinations had been made by numerous doctors with always essentially the same conclusions, either functional gastrointestinal complaint or neurasthenia. Objectively nothing significant was found on physical examination. So one was tempted to agree with previous diagnoses. We felt that roentgenographic examination of the stomach should be repeated and that it should be done extremely thoroughly and by a most expert roentgenologist. After all the diagnosis depended entirely on his findings. This examination revealed a diverticulum 1.5 centimeters in diameter arising from the second portion of the duodenum and a second large diverticulum 3 centimeters in diameter near the ligament of Treitz. At 4 hours these diverticula remained filled with barium and shadows were noted suggesting probably another large and a small diverticulum in the jejunum.

At the operation a large diverticulum near the ligament of Treitz was excised and the stump inverted with No. 00 chromic catgut and interrupted fine silk sutures. Two smaller diverticula in the jejunum were inverted with interrupted silk sutures. Air was then injected into the duodenum by means of a needle and syringe (Fig. 4). This procedure helped to locate the diverticulum in the second portion of the duodenum. It originated from the pancreatic surface and extended into the head of the pancreas to the left of the duodenum. Without the aid of air injection this diverticulum would not have been found. The diverticulum was carefully dissected free from the pancreas and was inverted into the duodenum with interrupted fine silk sutures. Because its origin was so intimately associated with the ampulla of Vater it was felt that this was a safety measure and permissible since the diverticulum was not huge. The gall bladder was also removed because it was large and redundant. In the convalescence the patient had a subhepatic infection with resulting drainage for several weeks. Since operation, she has been entirely free of nausea for the first time in 12 years. She has gained weight, looks entirely well, eats her meals with pleasure and in every way has had a most gratifying result from her standpoint and from the standpoint of surgery.

We have no way of knowing whether her diverticula were discovered at previous examination and discounted as not being accountable for the symptoms or whether, due to inadequate roentgenographic studies, they were not then disclosed. With the generally existing attitude regarding duodenal diverticula either alternative may have been the cause of her failure to get into the hands of an able surgeon for 12 years.

CASE 4. C.McC. For over 14 years the patient, a man, aged 30 years, had been having recurrent gastric hemorrhages and postprandial epigastric pain occurring periodically with long periods of remission. He had had an operation (gastroenterostomy) 14 years ago which did not definitely affect the symptomatology. Most of the hemorrhages had manifested themselves as melena and had recurred many times. Two weeks previously dark bloody stools showed again. Pain had become more severe recently and was diffusely distributed all over the abdomen. Ulcer diet and antacids had not given the patient relief in this attack. The physical examination revealed little of note. The blood pressure was 115 millimeters of mercury systolic, 68 diastolic. Gastrointestinal roentgenographic series showed a gastroenterostomy with functioning stoma. A large diverticulum was found in the concavity between the first and second portions of the duodenum (Fig. 9). This diverticulum was the size of a satsuma, measuring 7 centimeters in transverse diameter. Six hour observations show retention of barium in the duodenal diverticulum.

Operation was performed December 20, 1946. A large diverticulum was found under the first portion of the duodenum. It was a true diverticulum with walls comprised of all layers of normal duodenum and it was a genuine not a pseudodiverticulum, i.e., it was not due to cicatricial contracture of an ulcer. A small stellate scar was noted on the anterior aspect of the duodenum just proximal to the diverticulum but there was no contracture nor stenosis of the duodenum. The first portion of the duodenum and the distal 45 per cent of the stomach was resected leaving the anterior gastroenterostomy intact. Usually we remove about 60 per cent of the stomach when doing a gastrectomy and this "limited" resection was performed to obviate the necessity of disconnecting a satisfactory gastroenterostomy stoma. The stoma was carefully inspected and seemed to be entirely free of disease. The end of the stomach was closed. Then after severing the peritoneum around

the esophagus the esophagus was pulled down and the diaphragm pushed up and 3 to 4 centimeters of the vagus nerves were removed.

Examination 2 months after operation finds him entirely well except for slight fullness after eating a large meal.

CASE 5. G.B.G., a white male, aged 64 years, had had attacks of indigestion for 25 years. For 2 months he had suffered rather severe almost continuous epigastric pain. He had had pain which was severe and which occurred soon after meals and lasted for several hours. It was not relieved by food. He also had several episodes of melena and hematemesis during this time. Roentgenographic examination with a contrast meal revealed a large ulcer crater on the lesser curvature side of the antrum about 2 centimeters above the pylorus. The roentgenologist stated that the ulcer had penetrated into the pancreas. Gastric retention of approximately 10 per cent was noted at the end of 6 hours.

At operation in addition to large gastric ulcer that had perforated into the pancreas there were 12 large diverticula in the first 12 to 18 inches of the jejunum (Fig. 2). All of the diverticula were on the mesenteric side. Some of the diverticula were larger in diameter than the jejunum itself. A gastric resection was performed and a section of the jejunum 12 inches in length containing most of the diverticula and all of the large ones were removed. An end-to-end anastomosis of the jejunum was accomplished. A Hofmeister type of reconstruction completed the procedure. The postoperative course was uneventful. At follow up 1 year later the patient reports that he is completely well.

CASE 6. J.H., a man, aged 44 years, had symptoms relating to his present illness for only 2 months. He complained of pains in the upper abdomen more severe in the epigastrium but radiating from the right lower quadrant or the left upper quadrant of the abdomen to the epigastrium. These pains were extremely severe. They were sporadic and transient but they bothered him a great deal so that he was willing to have anything done which would insure him relief.

Objective examination revealed very little of significance, merely slight tenderness in the epigastrium. The real diagnosis was made by means of x-ray. Roentgenographic gastrointestinal studies showed two large diverticula in the jejunum.

At operation 16 centimeters below the ligament of Treitz was a large diverticulum, a herniation of the mucosa on the mesenteric border. Another diverticulum was found 8 centimeters farther down the bowel. This one was 5 to 6 centimeters in diameter in the distended state. The fenestra in the muscularis which permitted these mucosal hernias were large and for that reason to remove the diverticula a segment of the jejunum containing both diverticula was resected. An aseptic end-to-end anastomosis was accomplished. The patient had an uneventful convalescence. He recovered and has been entirely relieved of his symptoms.

SUMMARY

Diverticula of the duodenum are by no means rare occurring in from 1 to 2 per cent of all patients who have roentgenographic studies made for gastrointestinal symptoms. Up until now the generally prevailing opinion in the profession is that these lesions are relatively innocuous and rarely, even though present, cause symptoms. Such is not the case. They frequently are responsible for symptoms of a very troublesome and sometimes of a very disabling character. Surgical operation to obviate the presence of these diverticula either by inversion into the intestinal canal or by actual removal cures the patient. The indications for operation are discussed and when duodenal diverticula large enough to cause residual pooling of barium are present, removal or inversion is indicated even though the patient is operated on primarily for a coexisting lesion, such as cholelithiasis, and though removal of the gall bladder is accomplished at the same time.

We have discussed the location, the etiology, the symptomatology, and diagnosis of these lesions.

Jejunal diverticula are much less common than diverticula of the duodenum and much more difficult to diagnose preoperatively. They may cause severe symptoms and surgical removal of them results in cure. They should not be regarded merely as incidental findings, an opinion which has been frequently expressed in the past. They probably warrant operation in a high percentage of cases in which they are diagnosed.

We have discussed the technical approach to diverticula of the duodenum and jejunum. In the past judging from reported cases these diverticula have frequently been missed at operation. We have described a new technical procedure of pumping up the duodenum with air to show diverticula which may be hidden, particularly those protruding into the head of the pancreas or into the retroduodenal area. This new procedure should insure their discovery at the operating table and thus facilitate their removal.

A group of 6 cases, 4 of diverticula of the duodenum and 3 of diverticula of the jejunum were reported by us. In all of these cases

operation was carried out and each patient was relieved of his symptoms.

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CARCINOMA OF THE LARYNX

Methods and Results of Treatment

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IN recent years, the frequency and seriousness of carcinoma of the larynx have become generally recognized, and physicians have developed an increasing interest in the treatment of this disease. As a matter of fact, the therapeutic measures designed to cure this condition have become sufficiently diversified to arouse genuine controversies in regard to policies of treatment. It is our opinion that no one method is superior to all others; on the contrary, the type of treatment to be instituted in any given case must be governed by the type and extent of the growth which is present. In support of this opinion, we wish to present the methods of treating carcinoma of the larynx at the Mayo Clinic and the end-results of such management. This presentation is based on a study of 568 patients who were treated for malignant laryngeal neoplasms at the clinic during a 10 year period, 1934 to 1943, inclusive (Fig. 1).

At the clinic, every patient with symptoms referable to the larynx is required to give a thorough history of his symptoms. Roentgenograms of the thorax, studies of the blood, urinalysis, serologic tests for syphilis and examination of the sputum, if indicated, are made and a general physical examination is performed. The larynx itself is examined by the indirect method and in many instances roentgenograms and tomographs of the larynx are obtained.

When on indirect laryngoscopy a lesion of the larynx is found to be fungating or ulcerated, to cause fixation of a vocal cord or to produce a metastatic mass in the neck, there can be little question concerning the nature of the neoplasm. However, on mere visual inspection, many malignant laryngeal tumors cannot be distinguished from certain benign growths, tuberculomas, or syphilomas. For instance, early laryngeal epitheliomas of a projecting papillary character that have not infiltrated deeply enough to cause fixation of the vocal cord may be confused with benign papillomas. Papillary inflammatory growths often are more difficult to distinguish from papillary carcinomas than are papillomas. Occasionally an early infiltrative carcinoma without ulceration on a mobile cord can easily simulate one of many types of benign tumor. Distinguishing clinically between papillary leucoplakia or epithelial hyperplasia and papillary epithelioma often is impossible; however, such a distinction is unnecessary since thickened leucoplakia and epithelial hyperplasia always should be considered malignant until proved otherwise by microscopic examination.

Because mere visual inspection by indirect laryngoscopy cannot offer an unerring diagnosis, it becomes evident that biopsy of every laryngeal tumor is absolutely essential. We believe that removal of a specimen for biopsy is carried out most effectively under suspension laryngoscopy. We use the Lynch suspension apparatus through which an excellent view of the larynx can be obtained; it leaves both hands of the surgeon free to manipulate such instruments as are necessary for obtaining the specimen.

On our hospital service, a specimen of tissue from the larynx obtained under suspension laryngoscopy is examined at once by the frozen section method. This enables a competent pathologist to give the surgeon a definite histologic diagnosis usually in a few minutes. An immediate microscopic examination of frozen sections of tissue while the laryngoscope is still in place has two distinct advantages. First, if the pathologist finds that the first specimen of tissue is unsatisfactory for diagnosis, another piece of tissue can be obtained without delay. Second, if a laryn-

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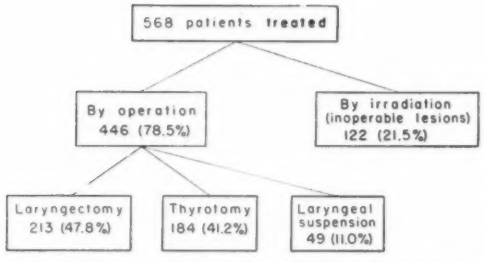

Fig. 1. Treatment of patients who had malignant laryngeal neoplasms from 1934 to 1943, inclusive.

geal growth is found to be malignant but meets certain specifications that will be discussed later, it can be removed or treated without delay.

It seems to us that close co-operation between the pathologist and the laryngeal surgeon is essential in treatment of carcinoma of the larynx. Not only is histologic examination of laryngeal tumors necessary in making an accurate diagnosis, but it is equally important in determining the degree of activity of malignant lesions. At the clinic carcinomas are graded, according to their microscopic appearance, from 1 to 4, grade 1 being the least malignant and grade 4 the most malignant (Broders' classification). The grade of malignancy is one of the very important factors in selecting the form of therapy most suitable in each individual case of carcinoma of the larynx.

It is our belief that the surgeon who assumes the responsibility of obtaining a specimen for biopsy from a laryngeal tumor should be competent and prepared to treat the lesion. If a specimen of tissue is removed by someone else before the surgeon sees the patient, it often is difficult for the surgeon to determine the extent of the lesion. Such a circumstance can jeopardize the patient's chance for a cure by a conservative operation; the surgeon, not knowing the exact limits of the growth, may find it necessary to perform a more radical surgical procedure than would have otherwise been necessary.

We would like to reaffirm our opinion that accurate diagnosis is essential in the care of malignant laryngeal neoplasms. Accurate diagnosis is based on thorough physical examination, indirect and suspension laryngoscopic examinations and detailed histologic examination of a specimen of the tumor.

TREATMENT

At the clinic, four methods are used for treatment of carcinoma of the larynx. They may be listed as follows: (1) thyrotomy (laryngofissure) and surgical removal of the growth, (2) laryngectomy, (3) removal or treatment of the local lesion under suspension laryngoscopy, and (4) external irradiation. The selection of the most suitable method in each individual case of carcinoma of the larynx is based on four factors: (1) size, location, and extent of the laryngeal growth, (2) grade of malignancy, (3) presence or absence of extralaryngeal extensions of the disease or metastasis to the cervical nodes, and (4) age and general physical condition of the patient.

All of these factors must be considered carefully in determining just what type of treatment should be employed in each case. Complete removal of the neoplasm is the prime consideration in any of the operative procedures, but unnecessary sacrifice of the voice should be guarded against. A radical operation should not be employed when a conservative one will remove the neoplasm equally well and will leave the patient with a good functional voice. On the other hand, a conservative operation should not be used when a more radical procedure is indicated as when the neoplasm is highly malignant and has probably extended beyond its apparent limits.

It always is a poor plan to try some conservative form of treatment with the assumption that, if the results are not good, something else can be attempted later on. This is detrimental to the patient's opportunity for a permanent cure as postirradiated cancer of the larynx is difficult to cure even by laryngectomy. It is well to remember that the patient who has a carcinoma of the larynx has but one good chance to get well, and if the first method fails, it is likely that subsequent methods also will fail. Consequently, the laryngologist should not use one form of treatment and then another in the hope that one of them will destroy the tumor completely. On the contrary, he should carefully consider in

each individual case all of the four factors previously mentioned and decide which method is most likely to effect a cure.

It is more or less generally accepted that low grade malignant tumors are radioresistant and, in consequence, are better treated surgically whenever possible. We believe that grade 1 or 2 carcinomas of the larynx which have not metastasized are treated more successfully by operation than by irradiation. Furthermore, in our experience, most grade 3 laryngeal cancers, if not too extensive, are also more likely to be cured by surgical means. Since about 93 per cent of laryngeal carcinomas are grade 1, 2, or 3 (Table I), it is evident that at the clinic the great majority are treated by surgical measures. It is our opinion that irradiation is the treatment of choice for grade 4 carcinomas of the larynx unless the lesion is small and well localized.

One argument sometimes advanced to discredit the surgical management of malignant lesions of the larynx is the immediate risk (hospital mortality) of such operations. However, as is shown in Table II, in 446 cases in which operation was performed at the Mayo Clinic from 1934 to 1943, inclusive, there were only 8 (1.8 per cent) hospital deaths. Furthermore, during the past 7 years, due to some refinements in surgical technique and due to the advent of sulfa drugs and penicillin, 428 patients were operated on for carcinoma of the larynx with only 2 (0.47 per cent) hospital deaths; and both of these deaths were due to coronary thrombosis. Consequently, we believe that the hospital mortality associated with surgical management of carcinoma of the larynx need be of no concern.

These hospital mortality rates are low as the direct result of several factors in addition to the two mentioned. Close co-operation between trained surgeons, assistants, and nurses at the time of operation and co-operation between the surgeon and physician anesthetists are contributing factors. We believe that the use of cervical block anesthesia rather than general anesthesia contributes to the lowness of our hospital mortality rate in major laryngeal operations (thyrotomies and laryngectomies). It is obvious, of course, that satisfactory block anesthesia can be effected only by a highly skilled anesthetist. Care given by specially trained assistants and nurses during the postoperative period of hospitalization also is a favorable influence.

TABLE I.—CARCINOMA OF THE LARYNX: 446 PATIENTS OPERATED ON; GRADE OF MALIGNANCY (BRODERS' METHOD)

Grade	Patients	
	Number	Per cent
1	64	14.4
2	212	47.5
3	139	31.2
4	26	5.8
Not stated	5	1.1
Total	446	100

THYROTOMY (LARYNGOFISSURE)

No definite rules have been set down for determining which malignant tumors in the larynx can be removed by thyrotomy and which should be treated by laryngectomy. Such a decision requires experience and surgical judgment. However, the type of tumor which is ideal for removal by thyrotomy is of a low grade of malignancy and is confined to the anterior two-thirds of a vocal cord which is freely movable. Carcinomas of similar type and location which have infiltrated the tissues of the cord a trifle so as to cause slight fixation of the anterior part of the cord usually still can be removed by thyrotomy provided that the portion of thyroid cartilage adjacent to the growth is removed along with the tumor. Extension of a low grade carcinoma across the commissure does not preclude the possibility of extirpation by thyrotomy. As a matter of

TABLE II.—CARCINOMA OF THE LARYNX: 446 PATIENTS OPERATED ON; HOSPITAL DEATHS*

Operation	Patients	Hospital deaths	
		Number	Per cent
Laryngectomy	213	4	1.9
Thyrotomy	184	4	2.2
Suspension laryngoscopy	49	0	—
Total	446	8	1.8

*During the last 7 years 428 patients were operated on; only 2 (0.47 per cent) of these patients died.

fact, superficial low grade epitheliomas involving the anterior half of both cords can be removed satisfactorily by thyrotomy; the result of such an operative procedure is a rounded opening in the posterior portion of the larynx which offers the patient an adequate airway and a fair voice. Small, well circumscribed, high grade epitheliomas confined to a portion of the anterior two-thirds of a freely movable vocal cord often are curable by wide excision and electrocoagulation through thyrotomy exposure.

Thyrotomy frequently is performed for exploration of the larynx to render the neoplasm visible; it often is impossible to determine preoperatively whether the growth should be removed in a conservative manner or whether laryngectomy should be done. Some well circumscribed supraglottic cancers, too extensive to be extirpated through a laryngoscope, can be removed by thyrotomy, although many require laryngectomy.

Briefly, the technique of thyrotomy employed at the clinic is as follows: We use cervical block anesthesia. We believe that it is preferable for the patient to be conscious during the operation because general anesthesia is difficult to control when the laryngeal lumen is exposed through an external incision and because any blood that happens to trickle down the trachea is coughed up readily. After cervical block, the thyroid and cricoid cartilages are exposed through a median line skin incision. With a motor-driven circular saw, the thyroid cartilage then can be divided in the midline and the cut edges retracted with hooks. Incision of the underlying laryngeal mucosa exposes the interior of the larynx and the neoplasm to direct view. The lesion is excised completely with a scalpel and scissors, and the underlying bed of tissue is electrocoagulated thoroughly. The tissue which was removed is sent immediately for histologic examination by the frozen section method. If a portion of the thyroid cartilage is contiguous to the base of the electrocoagulated area, it is removed with rongeurs.

This completes the removal of the growth. A tracheal cannula is inserted just below the cricoid cartilage to insure that the airway remains adequate during the postoperative healing period, a matter of 10 to 14 days. The wound is closed rather loosely with interrupted silk sutures and a split-rubber tube drain is inserted subcutaneously.

LARYNGECTOMY

At the clinic, all patients who have intrinsic laryngeal carcinomas which have infiltrated deeply enough to produce fixation of one or both vocal cords but which have not metastasized to the cervical nodes undergo laryngectomy provided that their age and general condition will permit. Some low grade carcinomas which show no clinical signs of metastasis but which have perforated the thyroid cartilage or the thyrocricoid membrane or have extended into the postcricoid region can be treated by laryngectomy with a good chance of permanent cure; in such cases, because the lesion is radioresistant, it would probably recur after irradiation. Furthermore, we have found that the possibility of curing a patient who has a low grade malignant lesion which is undergoing metastasis to the cervical nodes is greater when block dissection of the nodes and laryngectomy are carried out than when irradiation alone is given.

As was mentioned in the discussion of thyrotomy, small high grade epitheliomas on the anterior two-thirds of a vocal cord often can be removed satisfactorily by thyrotomy. However, unless they are extremely small, all high grade carcinomas involving a vocal cord should be treated by laryngectomy even though there be no fixation of the vocal cord. This assertion is based on the fact that very active epitheliomas often extend far beyond the apparent limits of the growth. If a high grade malignant laryngeal lesion shows any evidence of cervical extension or metastasis, much more will be accomplished by irradiation than by surgical measures.

In performing laryngectomy, we always employ local anesthesia by means of a cervical block. We do not favor use of general anesthesia for the reasons previously given in the discussion on thyrotomy. For surgical removal of the larynx, we prefer a median line skin incision to expose the thyroid and cricoid cartilages and anterior surface of the body of the hyoid bone. This incision is carried down be-

low the opening in the trachea. In order to facilitate exposure of the larynx, the body of the hyoid bone is divided at the midline by means of large bone forceps and the divided ends are drawn forcibly apart by claw retractors. The attachments of the muscles at the sides of the larynx are severed and the trachea is cut across. Usually, a tongue-shaped flap of laryngeal mucous membrane over the posterior part of the cricoid cartilage is elevated and left attached to the trachea; this flap ultimately aids in closure of the skin around the tracheal opening. The larynx, now detached from the trachea, is elevated and the pharyngeal mucous membrane is incised to expose the interior of the hypopharynx. By cutting across the thyrohyoid membrane, the larynx is freed completely.

On removal of the larynx, a triangular-shaped opening into the pharynx remains. This opening is closed by suturing its edges tightly in T-shaped fashion with two rows of interrupted catgut stitches. The skin margins of the wound are sutured with silk around the trachea and the flap of laryngeal mucous membrane previously described. Mattress silk sutures are used to approximate the skin edges just above the tracheal opening. After penicillin powder has been dusted into the wound, a double Penrose drain is inserted at the median line above the mattress sutures, and the wound is closed completely with interrupted silk sutures. For a few days postoperatively, the patient is given intramuscular injections of penicillin.

During recent years, there has been considerable controversy in the literature as to whether or not tracheotomy should be performed preliminary to laryngectomy. We believe that if the patient is young or middle aged, is in good health, and has a fairly adequate airway, there need be no hesitation in performing laryngectomy without preliminary tracheotomy. Removal of the larynx in one stage has two advantages. First, it saves the patient considerable time in hospitalization. Second, it is easier in many respects to remove the larynx when the patient has not undergone preparatory tracheotomy. If the airway of a patient who has a laryngeal carcinoma is badly obstructed, if his general health is poor, or if he is elderly, we believe that a tracheal cannula always should be inserted in advance of laryngectomy. When a cannula is inserted, removal of the larynx is postponed for 2 or 3 weeks after tracheotomy to permit all of the inflammatory reaction attending the tracheotomy to subside. It is important that there be no inflammation when laryngectomy is carried out.

SUSPENSION LARYNGOSCOPY

Destruction of certain laryngeal carcinomas with surgical diathermy under suspension laryngoscopy is advisable in selected cases. The choice of patients for this form of conservative treatment, however, should be made only by a laryngologist with extensive experience. Small low grade epitheliomas on vocal cords which are not fixed can be removed by surgical diathermy under suspension laryngoscopy with good results. Some laryngologists will perform thyrotomy to extirpate a very small inactive carcinoma that could have been removed by surgical diathermy under suspension laryngoscopy with much less risk and with just as good a prognosis. We wish to emphasize the fact that it is only small lesions on the vocal cords which can be treated occasionally in this conservative manner; if the neoplasm cannot be brought under direct view in its entirety or if there is any question as to the extent of the growth, thyrotomy should be performed.

In cases of low grade cancer of limited extent on the anterior two-thirds of the vocal cords of elderly patients who have hypertension, diabetes or bronchiectasis or in cases in which the patient's general physical condition is so poor as to contraindicate more radical measures, treatment under suspension laryngoscopy gives the patient a greater chance of a cure than could be expected if irradiation were used.

Well circumscribed and low grade malignant tumors of the epiglottis, aryepiglottic folds or base of the tongue can be treated with gratifying results by electrocoagulation under suspension laryngoscopy. After such a neoplasm has been removed by means of surgical diathermy, radon seeds often are inserted into the base of the lesion. Preliminary tracheotomy is carried out in all of these cases.

TABLE III.—CARCINOMA OF THE LARYNX: 5 YEAR SURVIVAL RATES ACCORDING TO TYPE OF OPERATION

Operation	Patients*		Lived five or more years after operation	
	Total	Traced	Number	Patients traced, per cent
Laryngectomy	104	88	53	60.2
Thyrotomy with excision or diathermy	95	73	61	83.6
Suspension laryngoscopy with excision or diathermy	28	24	22	91.7
Total	227	185	136	73.5

*Inquiry as of January 1, 1945. Included here are only those patients operated on 5 or more years prior to the date of inquiry; that is, 1939 or earlier.

Highly malignant neoplasms of limited extent involving the epiglottis, base of tongue and occasionally the postcricoid region often can be treated under suspension laryngoscopy by implantation of radon seeds and supplementary external roentgen therapy is given; it is surprising how frequently satisfactory results are obtained in such cases with this combined form of therapy.

In treatment of laryngeal carcinoma under suspension laryngoscopy, the pharynx and larynx first are cocainized thoroughly. Then pentothal sodium is given intravenously and oxygen is administered through an intranasal tube that extends into the pharynx. Adjustment of the suspension apparatus offers an excellent direct view of the interior of the larynx. The surgeon has both hands free to insert and manipulate those instruments which are necessary to obtain a specimen for biopsy, to destroy a lesion by surgical diathermy or to implant radon seeds.

IRRADIATION

At the clinic irradiation of laryngeal carcinomas is a form of therapy reserved for high grade, radiosensitive lesions which are too extensive to warrant treatment by surgical measures. Administration of roentgen rays in fractional doses is extremely important in the treatment of some carcinomas of the larynx; many high grade tumors in which surgical operations would be of no value can be cured by fractional roentgen therapy. However, we have found that only a small percentage of laryngeal cancers are highly active growths and, in consequence, we employ irradiation as a primary form of treatment rather infrequently.

The only low grade neoplasms which we treat by irradiation are those which are too extensive to be removed surgically and those which occur when the patient's age or general physical condition will not permit of surgical therapy.

In the majority of cases of carcinoma of the larynx in which intensive roentgen therapy is to be used, preliminary tracheotomy is to be recommended whether or not the patient's airway is badly obstructed by the growth. If tracheotomy is performed, there need be no concern in regard to the patient's airway should this become obstructed by postradiation edema.

END-RESULTS OF TREATMENT

As previously stated, 568 patients were treated for carcinoma of the larynx at the Mayo Clinic from 1934 to 1943, inclusive. Of these, 446 or 78.5 per cent were treated by surgical measures; that is, by laryngectomy, thyrotomy or under suspension laryngoscopy; 122 or 21.5 per cent were treated by irradiation (Fig. 1).

Of the 446 patients who underwent operation, 213 or 47.8 per cent were treated by laryngectomy; 184 or 41.2 per cent by thyrotomy, and 49 or 11.0 per cent by suspension laryngoscopy in which surgical diathermy was employed to destroy the growth or in which radon seeds were inserted into the growth. Of the 446 patients who underwent operation, 90.4 per cent were males and 9.6 per cent females; 80.9 per cent were between the ages of 45 and 69 years, 12.6 per cent were less than 4 years of age, and 6.5 per cent were more than 69 years of age.

Of all patients who underwent operation and who could be traced, 73.5 per cent survived 5 years or more without recurrence of the growth (Table III).

Of the traced patients who were treated by laryngectomy, 60.2 per cent lived 5 or more years after operation; 46 per cent of the lesions were graded 1 or 2 and 54 per cent were graded 3 or 4.

Of the traced patients who underwent thyrotomy, 83.6 per cent lived 5 or more years after operation; 61 per cent of these neoplasms were graded 1 or 2 and 39 per cent were graded 3 or 4.

Of the traced patients treated by surgical diathermy or insertion of radon seeds under suspension laryngoscopy, 91.7 per cent lived 5 or more years after operation; of the lesions in these cases, 82 per cent were graded 1 or 2 and 18 per cent were graded 3.

Of the traced patients who were treated by irradiation, 6.9 per cent lived 5 or more years after operation (Table IV); of these patients, 46 per cent underwent preliminary tracheotomy.

The lower survival rate associated with laryngectomy is to be expected because all malignant lesions treated by this method were large, some had extralaryngeal extensions at the time of operation, and some eventually gave rise to metastasis. The high survival rate of patients treated under suspension laryngoscopy can be attributed to the fact that these patients were selected carefully and the lesions were of low grade. The low survival rate of patients treated by irradiation is to be expected since practically all of the patients had inoperable lesions, the majority of which were considered completely hopeless when first examined at the clinic. This low survival rate should not be considered as an indication of the therapeutic value of irradiation in the treatment of carcinoma of the larynx; physicians who elect the use of irradiation in cases which we would consider surgical doubtless can produce statistics which show a much higher survival rate than Table IV reveals.

TABLE IV.—CARCINOMA OF THE LARYNX: 5 YEAR SURVIVAL RATE OF PATIENTS TREATED BY IRRADIATION

Treatment	Patients*		Lived 5 or more years after treatment	
	Total	Traced	Number	Patients traced, per cent
Tracheotomy and irradiation	35	32	3	9.4
Irradiation	41	40	2	5.0
Total	76	72	5	6.9

*Inquiry as of January 1, 1945. Included here are only those patients treated 5 or more years prior to the date of inquiry; that is, 1939 or earlier.

COMMENT

We would like to express our conviction that carcinoma of the larynx is a curable disease, particularly when diagnosed accurately and early. However, we believe that no one form of therapy is superior to all others in the treatment of this disease. On the contrary, the type of growth in question, its activity, extent, and location and the age and general physical condition of the patient should be the factors which determine what type of treatment should be instituted in each individual case. In general, low grade laryngeal carcinomas should be treated by surgical measures while extensive high grade, radiosensitive tumors require irradiation. Successful surgical therapy for carcinoma of the larynx is not a question of operative technique alone but of the co-ordinated and collective efforts of the surgeon, pathologist, anesthetist, assistants, and nurses.

MONTEGGIA FRACTURES

An Analysis of Twenty-five Consecutive Fresh Injuries

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IN 1814 Monteggia was the first surgeon to describe 2 cases of fracture of the shaft of the ulna associated with which there was an anterior dislocation of the head of the radius. This combination of injuries has since been commonly called a Monteggia fracture.

The purpose of this paper is to discuss the injury, its complications, treatment, and to give the findings and results obtained from a series of 25 fresh Monteggia fractures treated on the Fracture Service of the Presbyterian Hospital, New York, from 1929 through 1944. The discussion will be limited to fresh cases, since space will not permit of a detailed discussion of old malunited ulnar fractures with long standing radial head dislocations except to cite the inevitable result if cases are improperly diagnosed and inadequately treated.

Though not a common one the injury is also not a rarity, yet it might seem so if one were to count only the fresh cases that come to the clinic for treatment. It is an extremely important type of injury because of the fact that the true diagnosis is often completely missed on clinical and even on roentgen examinations. To overlook or fail to recognize the associated radial head dislocation results in inadequate treatment, continued dislocation, possible ugly and permanent deformity, loss of lateral stability at the elbow, restriction of function, and oftentimes pain.

ANATOMY

The radius and ulna are held in contact with each other at their upper and lower extremities by strong ligaments that allow the radius to rotate upon the ulna. The orbicular (annular) ligament (Fig. 3, a) surrounding the head of the radius is represented by a thickening in the elbow joint capsule and holds the radius likewise in contact for its articulation with the capitellum of the humerus. This ligament, however, is not so strong as the interosseus membrane that joins the radius and ulna throughout almost the entire extent of their shafts. The mechanism of injury in these cases is almost always due to the application of direct force, as for instance a fall upon the posterior aspect of the forearm. The ulnar shaft becomes fractured and its fragments are angulated or displaced forward by the force thus applied. If the radius is not fractured at the same time, the force which thus tends to shorten the ulna, must disrupt one bone from the other. The interosseus membrane being stronger than the orbicular ligament and at greater advantage owing to its longer attachment helps to lever the head of the radius away from the upper ulna and capitellum.

The mere fact that only one bone is fractured and angulated should make the physician or surgeon first examining the patient wonder what has happened to the other bone. The dislocation of the radial head is most commonly missed because of the very obvious fracture of the ulna and lack of awareness that with such a fracture one can never rule out radial head dislocation without good lateral roentgenographic views of the elbow joint. It should be *axiomatic* for the surgeon to assume that the radial head must be dislocated with this fracture unless it can be proved otherwise by adequate roentgen examination of the elbow. It may even be advisable in children to make comparative roentgenograms of the normal elbow. There should be no difficulty in determining whether or not the radial head is dislocated, because on studying a lateral roentgenogram a line drawn through the long axis of the radius should pass *directly* through the center of the capitellum or its epiphysis if projected upward regardless of the amount of flexion or extension present in the elbow joint (Fig. 1).

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INCIDENCE

Monteggia fractures are far more common in children than in adults. The ages of the 3 adults in this series was 27, 35, and 63 years, respectively. The ages of the 22 children ranged as follows: 3 years (1 case), 5 years (4 cases), 6 years (2 cases), 7 years (2 cases), 8 years (4 cases), 9 years (7 cases), 12 and 15 years (1 case each). There were 12 cases with this fracture in the right arm and 13 in the left arm. Three cases of the 25 did not come under our care until 5 days after injury; a fourth case sought treatment after 2 days. All of the other 21 cases came to the Emergency Ward within a few minutes to 3 hours after their injuries. The injury is usually caused by direct force, such as a fall upon the posterior aspect of the ulna or by being hit here, not infrequently by an automobile. The direct force thus accounts for the frequency of compound fractures of this type reported in the literature.

PHYSICAL EXAMINATION

The patient with a fresh injury usually holds his elbow partially flexed and in approximately mid-rotation. There is a depression or concavity over the posterior aspect of the ulna at the site of the fracture. The radial head can be felt displaced toward the anterior or anterolateral aspect of the elbow. Swelling, tenderness, and ecchymosis will be present or absent as in any other acute fracture depending upon the duration of the injury, displacement of the bones, and the degree of soft part damage.

TYPES OF FRACTURE AND DISPLACEMENT

There are in general two types of deformity in fresh injuries: (1) anterior angulation of the ulnar fragments associated with anterior dislocation of the radial head (Figs. 2, a, b, c); (2) lateral angulation of the ulnar fragments associated with lateral dislocation of the radial head (Fig. 2 d). *An additional possibility*—(3) posterior angulation of the ulnar fragments associated with posterior dislocation of the radial head (Fig. 2 c). Watson-Jones describes this third type but shows no roentgenograms. Naylor also describes it, but his roentgenogram shows a fracture of the radial head in addition to its dislocation. In none of the 25 cases of fresh Monteggia fracture discussed in this paper has a single incidence been found of this posterior dislocation without fracture of the radial head. It is felt that posterior angulation of the ulna almost always results in fracture of the radial head or its epiphysis and that this particular type of injury is an entirely separate entity from a Monteggia fracture.

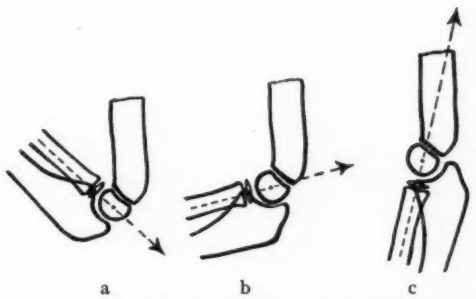


Fig. 1. Sketches of lateral views of bones at elbow in full flexion, midposition, and in full extension to demonstrate that longitudinal axis of radius normally passes through the center of the capitellar process or its epiphysis.

The fracture in the ulna is usually located in the upper third of the shaft, but it may occur as far distal as the junction of the middle and distal thirds. It may also occur just below the olecranon process. The type of fracture may be of the greenstick variety or transverse. It may be oblique or comminuted.

The common dislocation of the head of the radius with this type of fracture is in an anterior direction. Less commonly it is seen to have been dislocated in a purely lateral direction. In such a displacement of the radial head, the angulation of the ulna is always with its apex pointing laterally. Not uncommonly the radius is found to be dislocated in an anterolateral direction.

COMPLICATIONS

Compounding of the ulnar fracture is not too uncommon. Paralysis of the posterior interosseus nerve is of rather frequent occurrence of which more will be said further on. Nonunion may occur in adults at the site of the fracture, requiring later operative procedures for correction.

The greatest complicating factor in the opinion of the author is the possible and not

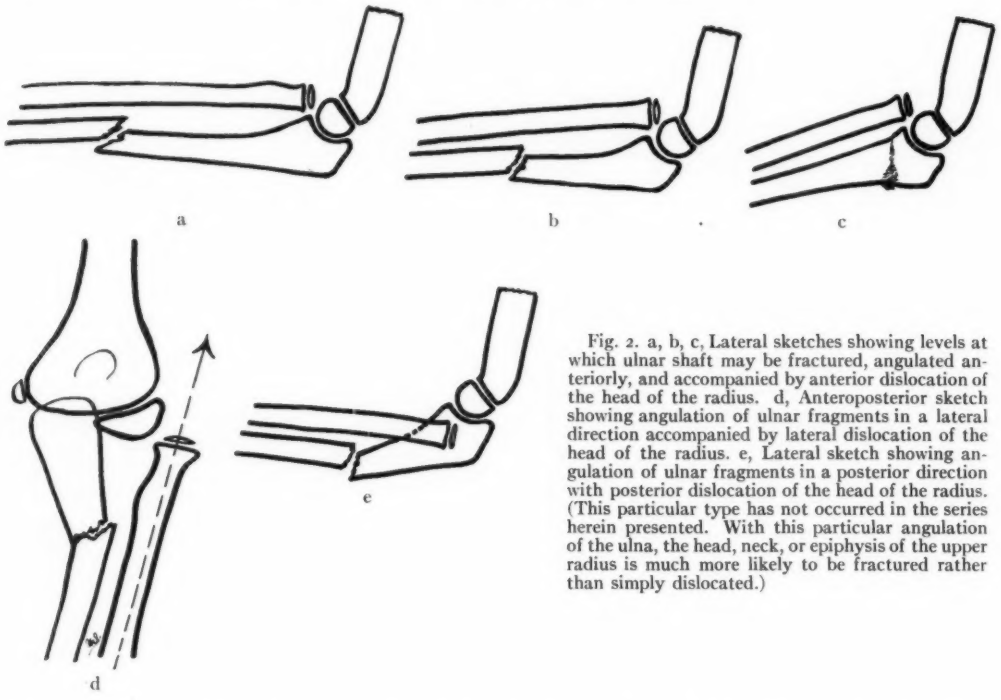


Fig. 2. a, b, c, Lateral sketches showing levels at which ulnar shaft may be fractured, angulated anteriorly, and accompanied by anterior dislocation of the head of the radius. d, Anteroposterior sketch showing angulation of ulnar fragments in a lateral direction accompanied by lateral dislocation of the head of the radius. e, Lateral sketch showing angulation of ulnar fragments in a posterior direction with posterior dislocation of the head of the radius. (This particular type has not occurred in the series herein presented. With this particular angulation of the ulna, the head, neck, or epiphysis of the upper radius is much more likely to be fractured rather than simply dislocated.)

infrequent interposition of a part or the whole of the orbicular ligament between the dislocated radial head and the capitellum which prevents its reduction by any closed manipulation.

PATHOLOGY OF ORBICULAR LIGAMENT

When the radial head becomes dislocated in this type of injury the orbicular ligament may show one of three types of pathology, all of which have been observed at open operation (Figs. 3, 4, 5, and 6). The ligament may become torn across and remain open. It may become torn across and fold in behind the radial head, thus preventing complete reduction of its dislocation and permitting subsequent loss of reduction. Third, instead of the radial head tearing through the orbicular ligament, it may be pulled out from beneath it and come to lie anterior to an intact ligament. In such case no reduction of the dislocated radial head is possible by closed or open methods until the ligament is incised vertically or is pried back over the radial head by an elevator after the fashion of using a shoe-horn. Roentgenograms are of little or no assistance in helping to determine the nature of the pathology of the orbicular ligament.

The following quotations from the operative reports of 2 cases will serve for illustration by describing the pathology and method of reduction of the radial head.

"The radial head lay in contact with the capitellum and the anterior portion of the capsule and the orbicular ligament was intact except for the lower margin of the latter which presented a sharp free edge. The radial head evidently had pulled down and out of the orbicular ligament. Reduction was performed by strong traction, increasing the anterior angulation and firm pressure made over the radial head while the capsule was lifted over it with an elevator." (Case 6.)

"The radial head had torn through the capsule distal to the orbicular ligament and had pulled out from beneath it. It was impossible to reduce the radial head without first dividing the orbicular ligament. The posterior interosseus nerve was displaced anteriorly by the dislocated radial head which caused pressure upon it."

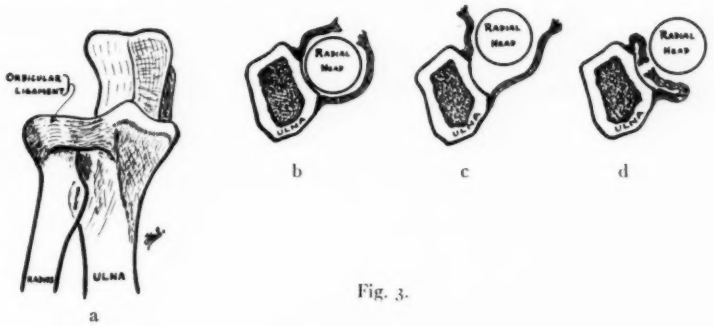


Fig. 3.

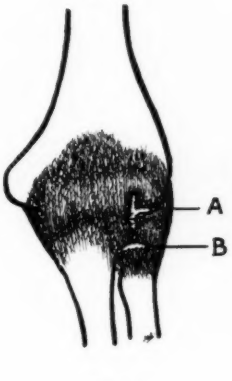


Fig. 4.

Fig. 5.

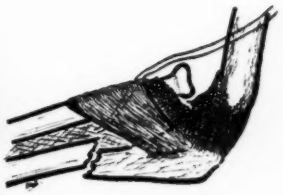


Fig. 6.

Fig. 3. a, Sketch showing normal relations of upper radius and ulna and orbicular ligament. b, c, d, Cross-sections at level of superior radioulnar joint showing torn orbicular ligament and its possible relations to the head of the radius.

Fig. 4. Sketch of anteroposterior aspect of elbow joint showing possible sites of tear in capsule which allows dislocation of radial head: a, through main capsule; b, below orbicular ligament.

Fig. 5. Sketch of anteroposterior aspect of elbow joint showing how radial head may become dislocated anteriorly by tearing capsule distal to orbicular ligament and pulling out from beneath it. The radial head then lies upon the intact main portion of the ligament, and the latter must be incised in order to bring about reduction of the radial head.

Fig. 6. Sketch of lateral aspect of elbow joint showing an anteriorly dislocated radial head (with Monteggia fracture). The radial head may lie anterior to an intact or partially intact orbicular ligament. The posterior interosseus nerve may be subjected to pressure or stretching by the displaced radial head before it enters the interval between the superficial and deep layers of the supinator brevis muscle to pass into the posterior compartment of the forearm. This was noted in Case 14 of this series; on admission patient showed no paralysis of this nerve, but 3 hours later did show paralysis. No attempt had been made to manipulate and reduce the fracture and dislocation.

This patient had no evidence of nerve palsy on admission, but developed it after 3 hours and was operated upon 18 hours after admission (Case 14).

TREATMENT

It has been stated by Boehler that all of these radial head dislocations can be reduced and held reduced by closed manipulation and immobilization in plaster. This would seem very doubtful in view of the above described pathology, and one might doubt very much if the cases analyzed in this article had a monopoly on such pathology whether the patient is treated by open or closed methods.

There is no single method of treatment applicable to all cases. Many undoubtedly can be reduced by closed methods, remain reduced, and achieve excellent results. These are the cases in which the ulnar fragments can be reduced and locked and in which the orbicular ligament is open and not folded in behind the radial head. Reduction should be tried by traction with the forearm extended. Firm pressure should be applied over the anterior aspect of the angulated ulnar fragments and as well over the radial head. When the latter slips back into place, the elbow should be flexed and then extended again. If the orbicular ligament is not interposed, the radial head should stay in place provided the ulna is adequately reduced (Fig. 7 a, b, c). If it remains in position the forearm should then be flexed to 90 degrees and immobilized in anterior and posterior molded plaster splints extending from the axilla to the metacarpophalangeal joints. The position of the radial head and of the ulnar fragments should receive weekly or biweekly roentgenographic checkups, and *if either one becomes displaced*, open operation should be performed and internal fixation used. If the original reduction has not been completely successful from the standpoint of either perfect reduction of the radial head or of the ulna, we believe that open reduction should be performed.

Not infrequently, even with successful closed reduction of both lesions, a loss of position of one bone occurs with resultant loss of position of the other. The ulnar fragments tend to bow anteriorly and toward the radius and in an adult, if not corrected, show a strong tendency to develop nonunion or malunion. We believe that all adults with this injury should be operated upon, have the ulna plated rigidly where possible and the radial head reduced and the orbicular ligament repaired (Fig. 8, a, b, c; Fig. 9, a, b). If the ulnar shaft is so comminuted as to make rigid fixation by a plate and screws an impossibility, it may be advisable to resort to intramedullary fixation by means of a Steinmann pin, Kirschner wire, or a small caliber Kuntschner nail inserted downward through the olecranon process. If this form of fixation is to be employed, it is advisable to expose the fracture site rather than take a chance of guiding the pin "blindly" into the medullary canal of the main lower fragment.

It is justifiable to attempt closed reduction in young children, but if this is not completely perfect or does not remain so with frequent check-ups, they should not be allowed to go more than 10 days or 2 weeks without operative correction. Small narrow stainless steel forearm plates are the best form of internal fixation for the ulna. It is just as important to prevent subsequent bowing of the ulna in a child as in an adult if subsequent subluxation of the radial head is to be avoided (Fig. 10, a, b, c).

Compounding of the ulnar fracture should call for immediate and thorough operative débridement and lavage with normal physiological saline solution. The fracture should be anatomically reduced and rigidly immobilized. There is no contraindication to the use of internal fixation provided the surgeon is properly equipped and trained to use it and provided that the wound is of less than 12 hours' duration and not infected. The wound should be *very loosely* packed open with fine mesh, plain gauze rather than taking a chance on primary closure. After 5 or 6 days the patient should again be taken to the operating room, the wound inspected, and if clinically clean, a secondary closure should be done after mobilizing the skin flaps in order to prevent the creation of any tension in the wound. Penicillin may be given *only* as an adjunct to thorough surgery, but *never* as a substitute. Compound fractures in the upper extremity are entirely different problems from those in the lower extremity and very rarely become infected if proper surgical principles and thorough and adequate débridement are carried out.

OPERATIVE INCISION

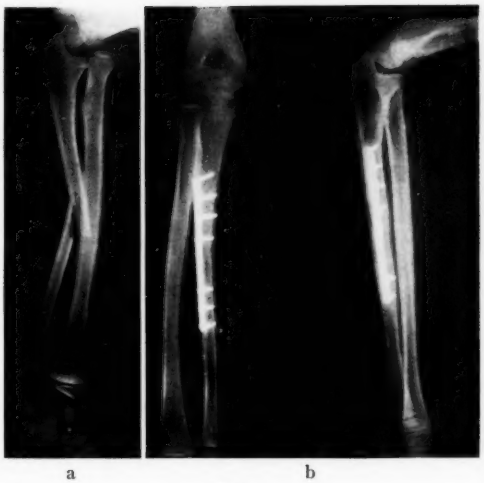
The choices of incision for the operative approach are several in number. The ulnar fracture site may be approached through an incision directly along the posterior subcutaneous crest of this bone and the radial head dislocation may be approached through a separate anterior incision of the Z-type, care being taken to avoid cutting directly across the flexion crease of the elbow in order to avoid development of a keloidal, contracted skin

a b c

Fig. 7.

a b c

Fig. 8.



a b

Fig. 9.

Fig. 7. Case 10. a, Original lateral view of forearm and elbow. b, Lateral view in plaster immediately after closed reduction. c, Anteroposterior and lateral views 3½ weeks after closed reduction showing healing of ulna with slight angulation, but maintenance of reduction of radial head.

Fig. 8. Case 16. a, Original lateral view of forearm and elbow. b, Lateral view after closed reduction. Ulnar fragments are improved, but not perfectly reduced. Radial head appears still dislocated. The diagnosis was initially missed. The elbow was operated upon 4 days later and a portion of the anterior capsule was found interposed between the radial head and capitellum. c, Lateral view 2 years after open reduction and fixation of ulna with three screws. (This form of internal fixation is not the most ideal. A narrow plate and screws would have been more satisfactory.) Radial head remains reduced.

Fig. 9. Case 24. a, Lateral view showing ulnar fracture at level of midshaft with anterior angulation. Radial head is dislocated anteriorly. Note how latter could easily have been overlooked had the elbow joint not been included on the film. b, Lateral and anteroposterior views 3 years and 4 months after open reduction and internal fixation of ulna with plate and screws. Radial head remains in normal position.

a b c

Fig. 10. Case 14. a, Original lateral view showing greenstick fracture high up in upper third of ulna with forward angulation and with anterior dislocation of radial head. (The radial head was found at operation to have pulled out from beneath the orbicular ligament.) b, Original anteroposterior view of same case showing ulnar fragments angulated laterally as well as forward and with lateral as well as forward dislocation of the head of the radius. c, Lateral view 2 years and 5 months after operation. No internal fixation was used to maintain position of the ulna after reduction. It was necessary to divide the orbicular ligament to permit reduction of the radial head and this was then sutured. Position of the ulnar fragments reangulated slightly and partial subluxation of the radial head recurred.

scar. The deep fascia is incised longitudinally in the interval between the brachioradialis laterally and the biceps and brachialis anticus muscles medially. As this interval is deepened, the superficial radial and posterior interosseus nerves are seen branching from the main radial (musculospiral) nerve. Since all muscular branches from the nerve pass in a lateral direction, the whole nerve should be retracted laterally in order not to harm any of these. The dislocated radial head and anterior capsule of the elbow joint are then readily seen and reduction and operative repair can be easily carried out as is necessary.

A single incision, as described by Speed and Boyd, may be used and is an excellent one for taking care of the ulnar fracture and radial head dislocation at the same time. This incision begins about 1 inch above and lateral to the tip of the olecranon and then passes distally along the posterior aspect of the ulna as far as necessary. The muscles attached to the lateral side of the ulna, including the supinator muscle, are elevated subperiosteally, thus exposing the radiohumeral joint. If care is taken to hug the ulna with the periosteal elevator, there is no risk of injuring the posterior interosseus nerve which lies between the superficial and deep layers of the supinator muscle. Through this incision it is thus possible to plate the ulna and to repair the orbicular ligament after reducing the dislocated radial head.

ANALYSIS OF CASES

There were 25 fresh Monteggia fractures in this series. Three were in adults, in one of which the fracture was compounded, the victim having been struck by a car. The majority of the children were injured at some form of recreation, roller skating being the single greatest factor. Posterior interosseus nerve palsy was noted in 6 cases on admission. Five others developed palsy following operation. All of these patients with nerve complications recovered. The original diagnosis was correct in 21 cases and missed in 4. Two of these were in the first 2 cases of the series. One was picked up after a week, but refused operation (Fig. 11) and did not return after 1 month of treatment. The second was not picked up until he returned to the follow-up clinic 4 months after injury (Fig. 12). This case has been subsequently followed for almost 13 years. The radial head is still dislocated and prominent. He works as a clerk without handicap, but

Fig. 11.

Fig. 12.

Fig. 13.

Fig. 11. Case 1. Anteroposterior and lateral views 2½ weeks after injury showing transverse type of fracture in ulna with angulation in anterior direction and with complete dislocation of head of radius. Early callus is seen at ulnar fracture site. This patient refused operation.

Fig. 12. Case 2. Lateral view 7 years and 9 months after injury showing late deformity of ulna, which has healed with persistent anterior dislocation of the head of radius. This latter dislocation was originally overlooked and not discovered until it was too late to correct. (Late unreduced radial head dislocations if causing pain or disability may be benefitted by resection of the radial head.)

Fig. 13. Case 13. Original lateral view showing simple greenstick fracture of ulna with anterior angulation and anterior dislocation of head of radius. At operation the anterior joint capsule was found interposed between the dislocated radial head and the capitellum. The ulnar fragments were fixed with a plate and four screws.

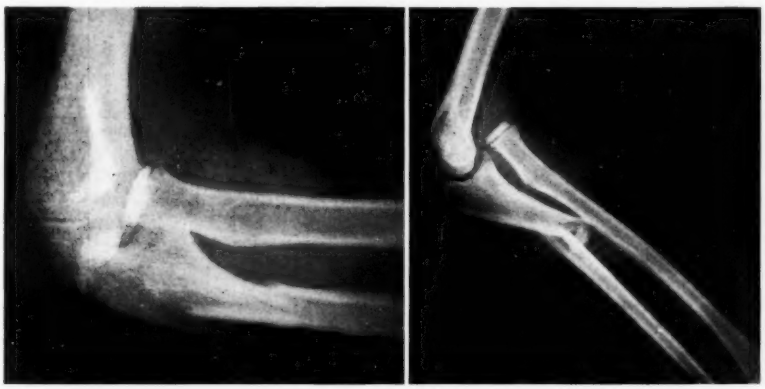


Fig. 14, left. Case 7. Original lateral view showing oblique type of fracture unusually high up in ulna and with anterior dislocation of head of radius. This patient was operated upon and the orbicular ligament was found open. The ulnar fracture was fixed internally with an aluminum plate and four screws.

Fig. 15. Case 22. Original lateral view showing fracture of upper third of shaft of ulna with slight comminution and with complete anterior dislocation of head of radius. Note also partial separation (fracture) of the distal radial epiphysis.

was unable to pass the physical examination for the sanitation department of the city of New York due to weakness and pain on heavy lifting. The 2 remaining patients who failed to have made on admission a diagnosis of radial head dislocation were picked up the following day and operated upon at 4 days (Fig. 8, a, b, c) and 1 day, respectively, both with excellent results after 7 and 5 year follow-ups, respectively (Figs. 13, 14, and 15).

TABLE I.—SUMMARY OF CASES

Case No. Age in years	Duration of injury	Associated conditions or injuries	Original diagnosis		Primary treatment		Secondary treatment	Internal fixation of ulna	Orbicular ligament untorn or folded in behind dislocated radial head	Radial nerve palsy		Follow-up and result	Remarks
			Correct	Incorrect	Closed	Operative				Before operation	After operation		
1 35	5 days	—		+	+ Ulna only							None	Operation advised at 18 days. Patient refused. Did not return after 1 mo.
2 15	1½ hrs.	—		+	+ Ulna only							12 yrs. 10 mos. Fair	Radius still dislocated
3 9	1 hr.	—	+		+		Operation at 2 days	2 screws	+			6 yrs. 7 mos. Excellent	Screws removed 20 mos. later
4 6	20 min.	Compound-ulna	+		+		Operation at 6 days	Plate and 3 screws		+		3 yrs. 4 mos. Excellent	Radial nerve recovered at 2 mos.
5 27	1 hr.	Compound-ulna	+			+ stat.	Operation stat. Operation at 14 days for radial head	Plate and 4 screws	+		+	None	Did not return after 1½ mos. Radial nerve recovered at 5 wks.
6 5	2 hr.	—	+		+		Operation at 5 days	None	+		+	1 yr. 3 mos. Excellent	Radial nerve recovered at 25 days
7 12	1 hr.	—	+				Operation at 3 days	Plate and 4 screws				8 yrs. 5 mos. Excellent	
8 8	3 hr.	—	+		+							9 mos. Excellent	
9 8	20 min.	—	+		+							2 yrs. 3 mos. Excellent	
10 5	1 hr.	—	+		+							2 yrs. 2 mos. Excellent	
11 7	1 hr.	—	+		+		Operation at 4 days	1 screw and 1 silk suture				7 yrs. 3 mos. Excellent	Slight prominence over ulnar fracture site
12 5	5 days	Weak pulse, fingers contracted	+				Operation at 1 day	None	+		+	6 yrs. 3 mos. Excellent	Recovery of radial nerve. Slight increased carrying angle
13 9	15 min.	—	+		+		Operation at 4 days	Plate and 4 screws	+		+	6 yrs. 9 mos. Excellent	Slight loss of carrying angle. ? osteochondritis. Radial nerve recovered at 7 wks.
14 9	1½ hr.	—	+			+	Operation at 1 day	None	+	+		9 yrs. 2 mos. Excellent	Radial nerve recovered at 9 wks. Radial head slightly subluxed anteriorly
15 0	1½ hr.	—	+		+					+		7 yrs. 8 mos. Excellent	Radial nerve recovered at 4 wks.
16 3	45 min.	—		+	+		Operation at 4 days	3 screws	+		+	9 yrs. 3 mos. Excellent	Radial nerve recovered at 2 wks. Slight prominence of ulna
17 9	5 days	Diabetes	+			+	Operation at 1 day for radial head. Ulna reduced closed	None	+	+		7 yrs. 5 mos. Excellent	Radial nerve recovered at 8 wks.

TABLE I.—SUMMARY OF CASES—Continued

Case No. Age in years	Duration of injury	Associated conditions or injuries	Original diagnosis		Primary treatment		Secondary treatment	Internal fixation of ulna	Orbicular ligament untorn or folded in behind dislocated radial head	Radial nerve palsy		Follow-up and result	Remarks
			Correct	Incorrect	Closed	Operative				Before operation	After operation		
18 9	1 hr.	—	+			+	Operation stat. for radial head. Ulna reduced closed. Operation at 10 d. for ulna.	Plate and 4 screws	+	+		7 yrs. 7 mos. Good	Radial nerve recovered at 3 weeks. Slight dorsal bowing of ulna. Extension at elbow limited 5°
19 8	2 hr.	—		+	+		Operation at 1 day	Plate and 6 screws				4 yrs. 10 mos. Excellent	
20 5	½ hr.	—	+			+	Operation stat.	Plate and 6 screws	+			4 yrs. 9 mos. Excellent	Refracture of ulna through screw hole at 13 mos. Radius not redislocated. Operation, ulna replated. Plate removed 3 mos. later
21 9	1 hr.	Compound wrist and fracture of lower radial epiphysis	+				Operation stat. for wrist and ulnar shaft. Radius reduced closed	Plate and 4 screws				4 yrs. Excellent	Elbow perfect. Has growth disturbance at wrist
22 8	2½ hr.	Separation of lower radial epiphysis	+			+	Operation stat.	Plate and 6 screws				None	Died after operation of aspirated vomitus
23 7	2 days	—	+		+							2 yrs. 2 mos. Excellent	
24 9	½ hr.	—	+			+	Operation stat.	Plate and 6 screws	+			3 yrs. 4 mos. Excellent	
25 63	1½ hr.	Compound tibia. Head and abdominal injuries	+		+							None	Good reduction of ulna and radial head, but subsequently lost position of ulnar fragments in plaster at 5 wks. Transferred to Mental Hospital at 5 wks.

In 16 of the 25 cases closed reductions were attempted as the primary treatment and 7 of these patients subsequently were operated upon either for loss of position of the ulna or radius. In 9 cases, including 2 compound fracture cases, open reduction was the primary treatment. One compound fracture had only the ulna treated originally by operation and 14 days later open reduction was done on the radial head. One other patient had an open reduction performed on the radial head the same day of injury, but a closed reduction only was done on the ulnar shaft. The ulna subsequently became angulated, and at 10 days open reduction with plating was performed on it. This patient after 7½ years still has a slight prominence over the ulnar fracture site and a loss of 5 degrees of full elbow extension. The total number of operative cases was 16, and internal fixation of the ulnar fragments was performed in 12.

As for the orbicular ligament pathology noted at operation, in 10 cases there was found either an untorn ligament with the radial head pulled out from beneath it or a torn ligament or capsule interposed between the radial head

and capitellum or lesser sigmoid notch of the ulna.

The average duration of treatment for all cases was 8 weeks.

All but 4 of the 25 cases have been followed for periods of years, the average being 5½ years. The more recent cases were for a shorter period, of course. The results in the 21 followed cases have been completely perfect from the standpoints of anatomy, function, and economic status in 13 cases and good to excellent in all the others except in Case 2. None of the cases resulted in nonunion. All of the cases with nerve injury recovered full function. One case had a possible osteochondritis in the elbow after 6 years and 9 months as noted by a clicking noise on pronation and supination.

Two (Cases 16 and 20) subsequently refractured the ulna through the site of one of the screws used for internal fixation. In Case 16 patient did this 4 years after the original trauma and he was treated for this second injury conservatively with plaster splints. There was no redislocation of the head of the radius. In Case 20 the ulna was refractured 13 months after the original injury, but the radial head was not redislocated. Owing to the fact that the plate used for internal fixation originally also became broken, he was reoperated upon, the broken plate and screws removed, and the ulna was plated again. Solid bony union occurred and this second plate was removed 3 months later. (See Table I.)

SUMMARY

1. Early recognition of the radial head dislocation is the most important part of the diagnosis in Monteggia fractures.

2. Early treatment with completely perfect reduction of the fracture as well as the dislocation is necessary and this must be checked frequently by roentgenograms to rule out secondary loss of position of either bone.

3. Open reduction is frequently necessary if the ulnar fragments cannot be held in anatomical position.

4. Open reduction is often absolutely necessary to make possible reduction of the radial head and for removal of interposed ligament or capsule.

5. If open reduction is to be performed, it should be done early and preferably with rigid internal fixation applied to the ulna.

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NEURILEMMOMA OF THE PHARYNX

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WHEN Stout proposed the name "neurilemmoma" in 1935 for the specific tumor of peripheral nerve sheaths described by Verocay in 1910 (6, 7), there had been 194 cases reported in the medical literature in the previous 100 years, designated as neurinoma, perineurial fibroblastoma, Schwannoma, peripheral glioma, and by other less common descriptive terms. To these, Stout added 52 tumors from his own experience indicating that the tumor was not as rare as might be supposed from the small number of previously reported cases. Since that time, the numerous reports of the occurrence of neurilemmoma have confirmed his impression.

Although a neurilemmoma theoretically can arise in any portion of the body where a nerve sheath exists, the great majority of reported tumors have been described in specific anatomical regions where one is apt to find them with relative frequency. One of the more rare sites for the discovery of a neurilemmoma has been the pharynx. The number of reported cases is now 6 (1, 2, 5), including 3 which are more specifically retrotonsillar (2, 3, 4).

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During the past 9 years we have removed 5 neurilemmomas (3 in the past 3 years) which presented in the oropharynx or nasopharynx. Because of the comparative rarity of the neurilemmoma in the pharynx and the fact that several of these tumors, although too large to be removed endorally, were successfully removed through the neck, it seems worthwhile to record these cases.

Tumors in the nasopharynx are more often malignant than benign and of the benign tumors, neurilemmoma is certainly one of the less common. Inasmuch as the neurilemmomas are encapsulated by an expanded perineurium, unless the tumor is also traversed by bundles of fibers of the peripheral nerve itself, the surgeon may overlook the presence of the nerve from which the tumor arose. For this reason, it is often difficult to know the actual site of parentage of a neurilemmoma even after extirpation.

The precise point of origin of the tumors reported here is not known in each instance. However, all of the patients had initial symptoms referable to the pharynx, all had visible tumor presenting in the pharynx, and all came to operation, either by the endoral or external approach, after seeking otolaryngological consultation. It is quite possible, nevertheless,

Fig. 1. Gross appearance of the tumor in Case 1. The tumor has been bisected and the photograph shows the cut surface.

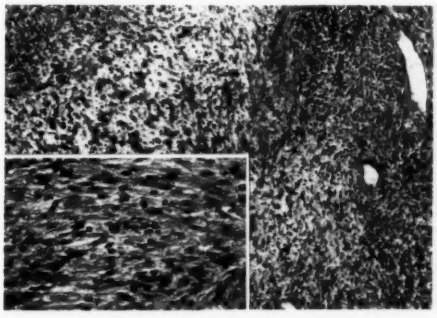

Fig. 2. Photomicrograph of the tumor in Case 1. Antoni types A and B tissue are both seen. Hematoxylin and eosin. × 70. The inset shows nuclear palisading. × 140.

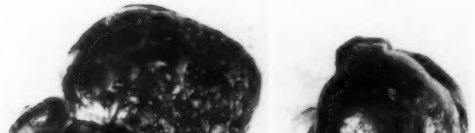

Fig. 3. Gross appearance of the tumor in Case 2. The photograph on the right shows the external aspect before sectioning, that on the left the cut surface.

that several of these tumors may have had their origins in the deep nerves of the neck, and, with growth, expanded under the pharyngeal mucosa. Neurilemmomas have been reported to have definite beginnings in the cervical sympathetics, in the roots of the spinal nerves and trunks of the cervical plexus, and in the spinal accessory and vagus nerves. Neurilemmomas arising from any of these sites finally could present themselves in the pharynx.

REPORTS OF CASES

CASE 1. N. F., a 49 year old white female, complained of a mass in the left side of the neck of 8 years' duration. Recently the tumor had been associated with occasional pain in the ear and a smaller mass had appeared in the tonsillar region.

Physical examination revealed a hard, nontender mass in the neck half the size of an orange which extended from the left ear to the level of the larynx. A similar mass 3 centimeters in diameter projected into the left side of the pharynx behind the posterior tonsillar pillar.

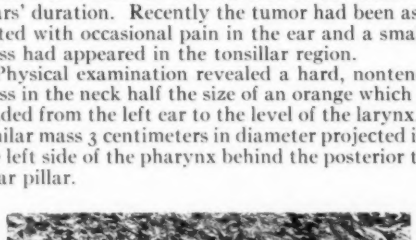

Fig. 4. Photomicrograph of a relatively well preserved portion of the tumor in Case 3. Masson's trichrome stain. × 150.

Roentgen examination of the neck showed, in addition to the soft tissue mass, questionable evidence of a destructive lesion involving the third to the sixth cervical vertebrae. A biopsy of the pharyngeal aspect of the tumor (Dr. Karl M. Houser) led to a diagnosis of neurilemmoma.

During the succeeding month intensive roentgen therapy was administered to the tumor in divided doses without apparent benefit. At the end of the roentgen therapy the pain in the ear was almost constant and the patient complained of difficulty in swallowing.

The tumor was removed (Dr. J. E. Rhoads) under endotracheal anesthesia through a lateral cervical approach. The removal was apparently complete except for a fragment of tumor tissue in the pharynx near the biopsy site. Convalescence was uneventful except for temporary partial paralyses of the hypoglossal and glossopharyngeal nerves. The patient was last contacted about 2½ years after operation, at which time there were no complaints or evidences of recurrence.

Pathologic examination: The biopsy (S.P. No. 50031) showed an unusually cellular tumor which also contained abundant fibrillar material. Types A and B tissues of Antoni were both present and nuclear palisading was a conspicuous feature.

Grossly the excised specimen (S.P. No. 50653) was a kidney-shaped, encapsulated tumor which measured 7 by 5 by 2 centimeters. It was firm and the cut surface was yellow and translucent, showing a few hemorrhagic areas. White, fibrous trabeculae partially separated the tumor into several lobules (Fig. 1). Microscopic examination revealed a picture essentially similar to that of the biopsy. The cellularity was striking and many of the cells were quite large and irregular (Fig. 2). Mitotic figures were not observed.

CASE 2. F. S., a 30 year old colored female, had complained of difficult and painful swallowing for 14 months. One year previously she had been studied in the Department of Otolaryngology for this same

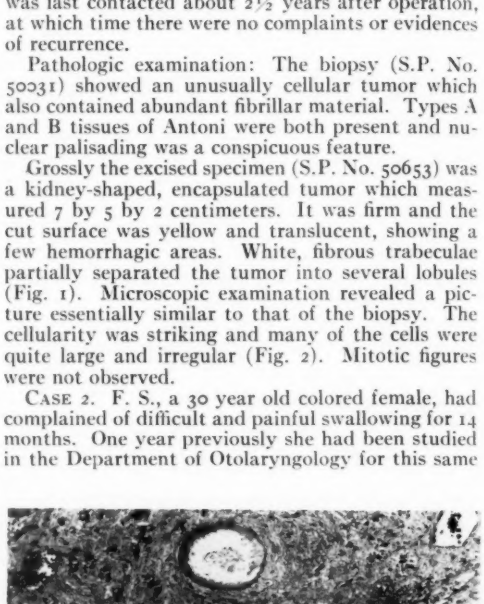

Fig. 5. Photomicrograph of the tumor in Case 5, showing an area characteristic of the neurilemmoma. Nuclear palisading is seen in the inset. Hematoxylin and eosin. × 70.

complaint. Biopsy of a pharyngeal mass detected at that time revealed no evidence of tumor. The Wassermann reaction was found to be positive but the pharyngeal tumor enlarged progressively despite intensive antiluetic therapy, until it threatened to obstruct her airway as well as prevent swallowing.

Physical examination revealed a hard "egg-sized" mass presenting on the left side of the posterior pharyngeal wall behind the tonsillar fossa. It extended up into the nasopharynx and down to the epiglottis and was not freely movable. An indefinite prominence was noted in the left submaxillary region. The pupils were irregular but reacted to light and in accommodation. Vision in the left eye was poor. There were no other significant physical findings.

At operation (C.E.K.) under endotracheal anesthesia the tumor was approached through an incision parallel to the medial border of the left sternocleidomastoid muscle. The tumor lay beneath some of the constrictor muscles of the pharynx and was shelled out by blunt dissection with the aid of a finger in the pharynx. It was encapsulated and seemed to arise from a small nerve trunk which was not definitely identified. The integrity of the pharyngeal mucosa was maintained throughout the procedure. Convalescence was uneventful. Three months after operation enophthalmos and ptosis of the eyelid were noted on the right side. One year after operation there was no evidence of recurrence and the motility of the pharynx was normal but the enophthalmos and ptosis persist.

Pathologic examination (S.P. No. 52729). Grossly the specimen was a soft encapsulated, ovoid tumor measuring 4.5 by 3 by 2.5 centimeters. Section showed a peripheral rim of translucent gray tissue but most of the tumor was friable and hemorrhagic (Fig. 3). Microscopic examination revealed both Types A and B tissues of Antoni, the former predominating. The tumor cells had small, dark, elongated nuclei, often arranged in palisade formation. Hyalinization and hemorrhage were prominent and many of the blood vessels were surrounded by thick collars of collagen. An additional section, prepared from what was thought to be the nerve of origin, showed numerous ganglion cells in addition to nerve fibers.

CASE 3. L.T., a 50 year old colored woman, complained of pain about the left thigh, hip, and lumbar spine, which had been present since she was injured in an automobile accident 6 months previously. Questioning elicited the fact that she had been having difficulty swallowing for the past several months. Physical examination showed, in addition to her orthopedic findings, a mass about 3½ centimeters in diameter in the right posterolateral wall of the oropharynx. It extended down into the upper part of the laryngopharynx. The right posterior tonsillar pillar was pressed forward and the tonsillar fossa was obliterated. The tonsil showed marked atrophy on this side. The mass was firm, circumscribed, and covered by normal mucosa. There was no cervical lymph node enlargement. Roentgen studies showed a soft tissue mass in the region described without evidence of bone destruction. Chest films revealed changes in the right lower lung field which suggested pleural thickening together with the presence of some fluid. The left lower lung field was also somewhat hazy and it was impossible to rule out the possibility of metastatic involvement.

On February 18, a biopsy of the pharyngeal mass was taken but the fragments submitted were too small for adequate examination. One area suggested the possibility of a neurilemmoma. Two subsequent biopsies were taken but none of them were satisfactory. It was the consensus that this was most likely a benign, radioresistant tumor and that the treatment of choice was surgical removal. After consultation with the surgical service it was decided to attempt removal by the oral route. A preliminary tracheotomy was done in preparation for the operation and the tumor was removed through the mouth under pentothal anesthesia. The tumor was well encapsulated and was shelled out readily by blunt dissection. Very little bleeding was encountered. The edges of the pharyngeal mucosa were approximated with catgut sutures. Penicillin had been started preoperatively and was continued through her postoperative course which was uneventful.

Pathologic examination (S.P. 54573). Grossly the specimen was an encapsulated tumor mass measuring 5.5 by 4.0 by 2.5 centimeters. Much of it was occupied by a central cystic cavity. Microscopic examination revealed that dense, relatively acellular fibrous tissue made up most of the cyst wall. Hyalinization, evidences of old hemorrhage and cystic degeneration were unusually marked and there were also foci of chronic inflammation. Despite the extent of these secondary changes, there were areas where the nuclear palisading and the loose, myxoma-like tissue characteristic of the neurilemoma, could be seen (Fig. 4). Several clusters of "foam cells" were noted.

A few ganglion cells were observed in the periphery of the tumor. These were presumed to be accidental inclusions, from a sympathetic ganglion or nerve which gave rise to the tumor.

CASE 4. D.O'r.[1] a 55 year old white male, complained of difficulty on swallowing and examination disclosed a large mass on the posterior pharyngeal wall just behind the right posterior faucial pillar. It was about the size and shape of a hen's egg and was covered by normal mucosa. The diagnosis of sarcoma had been made elsewhere and x-ray therapy had been instituted. This apparently had been without beneficial effect. A biopsy was planned but at operation the mass shelled out so readily that it was decided to administer a general anesthetic and remove the entire lesion. As the operation progressed it was discovered that the mass extended to the region of the carotid sheath and dissection became more difficult. One large vessel had to be ligated. This was apparently the internal carotid, although it was of unusually small caliber for that vessel. The mass was eventually removed and the patient's con-

[1]The hospital record of this patient was not available and the clinical abstract was taken from a report by Dr. Karl M. Houser.

dition appeared to be good when he was returned to the ward. However, he never regained consciousness and died 24 hours later. Permission for autopsy was not granted and the exact cause of death was not determined.

Pathologic examination (S.P. 23516): No gross description is available. Microscopic examination revealed an encapsulated tumor composed in part of compact fibrillar tissue and in part of loose textured areas poor in fibers. The cells had small, elongated and deeply stained nuclei, often arranged in palisades. Hyalinization and microcystic degeneration were striking features.

CASE 5. C.L., a 20 year old white male, was well until he developed an acute upper respiratory infection. He consulted his family physician who discovered a swelling in the right posterior pharyngeal region which he diagnosed as a peritonsillar abscess. The patient was kept in bed for 2 weeks and although all signs of the upper respiratory infection had subsided there was no change in the size of the pharyngeal mass. Three weeks after the onset of his illness, his tonsils were removed, but there was still no change in the size of the mass, and the patient was referred to the University Hospital.

Physical examination was negative except for the mass in the right side of the pharynx. It was smooth, nontender, nonfluctuant and covered by normal mucous membrane.

X-ray examination of the chest and neck was reported to show "a large soft tissue tumor occupying the oropharynx and nasopharynx."

The tumor was removed by the oral route (Dr. Karl M. Houser). There was considerable bleeding which necessitated packing of the cavity. Following removal of the packing there was no further bleeding or respiratory difficulty and thereafter convalescence was uneventful except for a transient right Horner's syndrome.

Pathologic examination (S.P. No. 29898): No gross description is available. Microscopic study showed the greater part of the tumor to be composed of relatively acellular collagenous tissue. Microcystic degeneration was noted. Palisading of the nuclei was a striking feature (Fig. 5).

The final diagnosis of these tumors cannot be made without histologic examination. The comparative frequency of the nasopharyngeal neurilemoma in our recent experience, however, led to the correct diagnosis preoperatively in 2 cases.

If the tumor, visualized and palpated in the pharynx by endoral examination, is of sufficiently small size to be removed safely through the mouth, preliminary biopsy, in our opinion, is not indicated. With the larger tumors, of diameter too great to permit removal safely through the mouth, we believed, at first, that preliminary biopsy was in order. However, biopsy of large tumors through the pharyngeal wall is not always satisfactory and safe. Furthermore, the biopsy site is a potential pathway for infection in the neck at the time of biopsy or later removal of the tumor by the lateral cervical approach. Our 2 most recent patients were operated upon (one through a lateral cervical approach and one endorally) on the basis of clinical diagnoses, subsequently proved to be correct. Biopsies were attempted in both cases but were of insufficient depth to be diagnostic.

In spite of the fact that benign tumors are less common than malignant ones in the nasopharynx, the signs of benignity of the neurilemomas here reported were definite. The round or fusiform shape of the tumors, their apparent encapsulation, and the fact that they do not ulcerate the pharyngeal mucosa or fix themselves to it usually are demonstrable signs.

Ehrlich and Martin recommend aspiration biopsy of these tumors and diagnosed a retropharyngeal and a retrotonsillar neurilemmoma by this method. Neither patient was operated upon, however, because it was considered an unjustifiably hazardous procedure for benign tumors with minimal symptomatology.

Difficulty in swallowing was the presenting symptom in 3 of our 5 patients. Four were also conscious of a mass but the presence of a mass in itself caused but one patient to seek medical care. Two of the tumors were found in patients who were under medical care for other reasons. Direct questioning disclosed that one of these patients had been aware of dysphagia but the other had no previous complaints attributable to the tumor. One patient had unequal pupils before operation. The histories presented by our patients would suggest that small, benign, asymptomatic neurilemmomas may eventually cause trouble and for that reason should probably be removed when encountered except in the face of specific contra-indications. Experience with Case 1 emphasizes again the resistance to radiation of the neurilemmoma, an observation which has been pointed out previously (2).

Three of the tumors in this group are characteristic examples of the neurilemmoma (5). A fourth, Case 1, has the usual histopathologic

features of the specific tumor of nerve sheath origin and is readily recognizable as such, although it is unusually cellular and the cells are frequently large, irregular, and hyperchromatic. However, mitotic figures were not observed and this patient has had no further difficulty in the 2½ years since operation.

The fifth tumor, Case 3, presents diagnostic difficulties. Similarities to the characteristic structure of the neurilemmoma are limited to fragmentary portions of the lesion. We believe that the degenerative changes so commonly seen in tumors of this type have, in this instance, been sufficiently advanced and widespread almost to obliterate the underlying structural features. The ganglion cells occasionally encountered in the periphery of this tumor are regarded as most likely to be inclusions from a sympathetic nerve or ganglion of origin rather than an integral part of the neoplasm.

SUMMARY

Five instances of neurilemmoma of the pharynx are reported, bringing to 11 the total number recorded in the literature. Four of the tumors in this group caused dysphagia, 1 of them being associated with respiratory difficulty in addition. In the 2 cases most recently encountered, the correct diagnosis was made preoperatively on the basis of clinical findings. We believe that even small, asymptomatic neurilemmomas should be removed surgically, since they may produce symptoms as they enlarge. Three of the tumors in this group were removed endorally, 2 through a lateral cervical approach. There was 1 postoperative death.

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COMPARATIVE HEMATOLOGIC FINDINGS IN NORMAL, SPLENECTOMIZED AND SPLEEN-TRANSPLANTED DOGS

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THE transplantation of the spleen as well as of other organs with anastomosis of blood vessels has been attempted by several investigators. Carrel (6) reported autotransplantation of the spleen of a dog and found that it remained in normal condition for more than 20 months after the operation. In another dog, however, the transplanted spleen had completely disappeared about 3 months following operation. On exploratory laparotomy 2 weeks after operation, occlusion of the artery has been found to be probable (7). The anastomosis of the vessels was made by the suture method of Carrel, and no account was found in the literature that such anastomosis of the transplanted spleen was made by a nonsuture method. The first described nonsuture method for organ transplantation has been given by Ullmann who used the prosthesis of Payr for anastomosing the vessels of the kidney with the carotid artery and the jugular vein. The prosthesis of Payr consists of magnesium tubes. Although Carrel succeeded in transplanting spleens, he did not attempt to transplant a second spleen. We employed the nonsuture method of Blakemore, Lord, and Stefko with vitallium tubes as prosthesis of the splenic artery and vein to the femoral or middle colic vein, respectively.

In an attempt to learn more about the physiologic functions of the spleen, we inserted this organ in other sites of the circulatory system and also attached a second spleen by homotransplantation in dogs. The displaced and sometimes increased spleens were studied by their effect on certain hematological tests. For the appraisal of the hematologic data we found it necessary to establish control values on a large number of healthy mongrel dogs. These findings were obtained in 20 comparative series on 16 dogs. In addition, we present hematologic data secured at various intervals of time following splenectomy of healthy dogs.

From the Laboratory of Cellular Physiology, Department of Biology, New York University, New York, and the Department of Surgery and Gynecology, School of Medicine, University of Virginia, Charlottesville, Va.

A. Operative methods. Through an upper left rectus incision, the great omentum is carefully displaced to the right. Exposure of the spleen is best accomplished by packing off the stomach medially. With the proper retraction the spleen presents itself in the wound and is readily delivered. The splenic artery and vein are identified, isolated, ligated, and divided between clamps. The remainder of the pedicle is then successively clamped, divided, and ligated. The spleen is removed and is immediately irrigated via the splenic artery with 100 cubic centimeters of warm physiologic saline containing 10 units of sodium heparin per cubic centimeter. This step is important and may mean success or failure of the procedure to follow.

In another animal the skin of the lower abdomen and upper inner thigh is carefully prepared. The operative field is cleansed with soap and water, treated with benzene, and carefully washed with alcohol and ether. It is then painted twice with iodine, and alcohol is applied to remove the latter.

A longitudinal incision, 7 centimeters in length, is made high in the thigh, starting 3 centimeters above the inguinal ligament and following the course of the artery downward. If the initial incision has been correctly placed, the muscle groove between the sartorius and abductor longus muscles can readily be identified. Access to the great vessels can easily be gained. The artery and vein are freed for a distance of 6 to 8 centimeters. They are individually clamped with rubber shod clamps at the proximal end and doubly ligated with medium silk at the distal end and then divided. The vessels are thoroughly irrigated with physiologic saline and then affixed with vitallium tubes (4). The spleen is now brought into

the field. The splenic artery and vein are anastomosed to the femoral artery and vein, respectively. It is important at this point not to damage the intima of either the splenic vessels or the femoral vessels, for such trauma may lead to thrombosis.

A small incision is made in the lower abdomen just above the inguinal ligament. This incision should be long enough to facilitate the entrance of the spleen into the abdominal cavity. Care must be taken not to cause any angulation or tension on the splenic and femoral vessels for this may lead to occlusion of the anastomoses. Such partial or complete occlusion may initiate thrombosis, as we observed in a number of operations previously. The vessels are swung over the inguinal ligament. In this manner, the palpatory method is employed to test the patency of the vessel daily.

The wound is closed by first closing the peritoneum with a continuous suture of fine silk and then approximating the fascia, subcutaneous tissue, and skin by means of interrupted sutures of fine silk. A collodion dressing is applied to the wound.

B. Hematological methods. The red and white blood counts and differential smears were made according to standard procedures. The sedimentation rate was done according to Westergren and hematocrit values were obtained with the method of Wintrobe in duplicate tests (32). The coagulation times were run at room temperature within 21 to 25 degrees C. Each cubic centimeter of blood tested in duplicates using pyrex tubes 10 by 100 millimeters. Platelet counts were made according to the Copley-Robb method (13, 14), 0.5 per cent solution of brilliant cresyl blue (national aniline NV-27) being used (9). Clot retraction was tested according to Aggeler, Lucia, and Hamlin (2) in duplicate tests. A correction was used for the clot volume in this test, since we had observed in some human blood a rather high red blood cell sediment following the incubation of the blood coagulum. This volume of sedimented cells is to be added to the volume of the coagulum for the determination of the proper serum volume. Furthermore, for determining the extracorpuscular volume, the coagulum and the sediment are taken as the volume from which the hematocrit volume is subtracted, thus giving a more accurate extracorpuscular volume. This correction may not be practical in all instances; however, it is necessary in all cases where a markedly increased sedimentation rate takes place.

The clot firmness was determined according to the method of Lalich and Copley (20). All clot firmness tubes were run in triplicate tests. Since tissue juice affects the coagulation time and firmness of the coagulum (20), blood was secured in a separate syringe for these tests. The same needle, placed *in situ*, was used for all blood withdrawals.

The alcogel test with serum was made with a slight modification as previously described by Copley (8). Two-tenths cubic centimeter of 80 per cent ethyl alcohol was added to 0.2 cubic centimeter of native serum, well mixed for incubation at 37 degrees C. The degree of gelation was recorded after 5 minutes' incubation time. The appearance of filaria was observed on a wet slide in citrated blood.

RESULTS

I. Clinical observations. A. Splenectomy.

Dog 844 and dog 814 had their spleens removed. The postoperative course of both animals was uncomplicated. Dog 814 developed a postoperative secondary anemia; this, however, subsided on the 31st postoperative day.

B. Autotransplantation of spleen.

Dog 818. In this animal the spleen was removed and transplanted to the left inguinal region. The splenic artery and vein were anastomosed to the femoral artery and vein respectively.

On the first postoperative day the spleen was found enlarged and firm on palpation. It occupied the lower half of the abdominal cavity. On the second postoperative day the animal was found dead in the cage. On gross examination the organs of the thorax appeared to be normal. Gross examination of the abdomen revealed the spleen to occupy the lower portion of the peritoneal cavity. The spleen was firm and markedly enlarged. It measured 20 centimeters along its axis, 2.5 centimeters in thickness, and 11.5 centimeters across its broadest points; weighing 500 grams. On cut section the organ emitted blood freely in large amounts. The anastomoses of the femoral and splenic vessels were found to be patent with no evidence of thrombosis. Postmortem diagnosis: splenomegaly.

Dog 846. In this animal the spleen was left attached to its usual pedicle with the exception of the

splenic vein which was anastomosed to the middle colic vein.

On the first postoperative day the spleen was palpable. The animal and the wound were in good condition. On the second postoperative day the animal was found dead in the cage. On gross examination at autopsy the left lungs were noncrepitant and infiltrated, while the right lungs appeared normal. Heart and greater vessels did not show any gross pathologic changes. Examination of the abdomen revealed an enlarged spleen, measuring 30.5 by 9 by 2.5 centimeters and weighing 500 grams. The anastomosis of the splenic vein and middle colic vein was found to be patent and did not show thrombi. The remaining organs of the abdomen did not show pathologic changes. Postmortem diagnosis: bronchopneumonia, splenomegaly.

Dog 67. In this animal the spleen was removed from its usual pedicle and transplanted to the left inguinal region. The splenic artery and splenic vein were anastomosed to the femoral artery and vein, respectively.

On the first postoperative day the animal was found in shock and was given an infusion of 300 cubic centimeters of 10 per cent glucose in saline. Approximately 200 cubic centimeters of sanguineous fluid was evacuated from the abdominal cavity. The spleen was palpated and found to occupy both lower quadrants.

On the second postoperative day the animal was found dead in the cage. The thorax and abdomen were examined on autopsy. Approximately 75 cubic centimeters of serosanguineous fluid was contained in the right chest. The right lungs appeared to show infiltration indicating lobar pneumonia. The left lung appeared to be normal on gross examination. No gross pathologic changes were in the heart and greater vessels. Examination of the abdomen revealed the spleen markedly enlarged occupying the lower abdomen and displacing the other viscera. It measured 30 by 7 by 1.5 centimeters and was firm and congested. The anastomoses of the femoral and splenic vessels were patent and it appeared that they were functioning prior to death. The remaining abdominal organs did not exhibit pathologic changes. Postmortem diagnosis: splenomegaly.

Dog 840. The spleen was taken from its pedicle and transplanted to the right inguinal region, the right femoral artery and vein being used as the source of blood supply. This animal survived the operation and was maintained for 31 days. An exploration was done on the 27th postoperative day at which time the spleen was found to be two-thirds its original size. The splenic vessels were palpable and pulsating, indicating patency of the anastomoses.

It might be stated at this point that at the time of transplantation, directly following the anastomosis 0.2 cubic centimeter of 1:1,000 adrenalin chloride was injected into the substance of the spleen to reduce enlargement and possibly any future development of splenomegaly.

C. Homotransplantation of second spleen. In two dogs, No. 845 and No. 849, a second spleen was incorporated. These spleens were transplanted to the femoral region of the recipient.

Dog 845. The spleen of dog 844 was implanted in dog 845 in the left inguinal region anastomosing the femoral vessels to the splenic vessels. This animal had a stormy postoperative course and expired on the second day after operation. At autopsy the spleen was found markedly engorged with blood and the peritoneal cavity was filled with serosanguineous liquid. Postmortem diagnosis: peritonitis, splenomegaly.

Dog 849. The spleen of dog 814 was transplanted into the left inguinal region. The femoral vessels were employed to anastomose to the splenic vessels. This animal, like dog 845, had a stormy course and died suddenly on the second postoperative day. At autopsy the spleen was found to be engorged with blood and the peritoneal cavity was filled with serosanguineous fluid. It could not be determined whether the anastomoses were patent. Postmortem diagnosis: Peritonitis, splenomegaly.

II. Hematologic findings. Tables I and II give data obtained in 16 healthy dogs. Twenty comparisons of hematologic findings are made. The red blood count varies from 6.21 to 8.47 millions. The hemoglobin varies between 12.5 to 18 grams per 100 cubic centimeters. The hematocrit ranges from 39 to 61 per cent. The erythrocyte sedimentation rate (Wintrobe) after 60 minutes was found to be zero in 10 tests, whereas the remaining ones showed variations from 2 to 21 millimeters. The coagulation time at 21 to 25 degrees C, varied from 1.5 to 6 minutes. Platelet counts ranged from 200,000 to 360,000. All tests for clot retraction showed differences between 36 and 59 per cent serum volume. The extracorpuscular volume was zero in 3 tests and varied from 3 to 22 per cent in the remaining tests. The clot firmness was found in 14 tests to be between 65 and 145 millimeters mercury and in the remaining 6 tests ranged between 160 and 395 millimeters mercury. The white blood count differed from 7,000 to 16,400. This variation was found at 2 days' interval in dog 845. The differential white count differed considerably. Nonsegment forms differed from 1 to 12 per cent in 19 tests and in one dog 33 per cent were found. Lymphocytes ranged from 13 to 61 per cent and monocytes were found in 18

TABLE I.—TWENTY COMPARISONS OF VARIOUS HEMATOLOGIC FINDINGS OBTAINED FROM 16 HEALTHY DOGS

Dog number	Hemoglobin gm.	Hematocrit per cent	Sedimentation Rate 60 min., mm.	Alcogel test 5 min., 37° C.	Coagulation time in min. (21–25° C.)	Platelet count in thousands	Clot retraction		Clot firmness mm. Hg	Filaria
							Serum vol. per cent	Extracorpuscular volume per cent		
851	15.0	52	2	o	1.5	250	44	4	160	o
67	18.0	44	o	o	5	230	38	18	65	o
840	16.5	54	o	o	3	230	36	10	88	o
818	18.0	61	o	o	4.5	205	36	3	105	
849	14.0	54	o		3.5	360	43	3	180	
814	14.0	50	o	o	3.0	290	38	12	65	o
825	13.5	43	15	o	6	215	53	4	135	o
833	14.5	44	o		3.5	200	58	o	98	
846	14.5	48	8	o	3.5	220	46	6	140	
850	13.5	39	12	o	2.5	250	39	22	395	o
49	16.0	55	o	o	2.5	225	42	3	75	o
44	14.5	48	12	o	2	220	47	5	220	o
819	14.5	49	o	o	4.5	210	48	3	145	o
						215				
852										
1. day	13.5	45	15	o	5	255	42	13	270	o
19. day	13.5	45	21	o	6	215	42	13	305	o
844										
1. day	17.0	59	o		2	220	36	5	120	o
2. day	17.0	55	o	o	2	240	41	4	125	o
845										
1. day		42	12	o	3.5	250	59	o	124	
3. day	12.5	42	16		4	250	58	o	105	
5. day	12.5	40	5	o	2.5	285	54	6	104	+

o=Negative +=Present

tests amounting to 1 to 9 per cent. In 11 tests no eosinophils were counted and in 6 tests they ranged from 1 to 3 per cent and in the 3 remaining, they were 13 to 16 per cent. No basophils were found in 17 tests, the 3 remaining had 1 to 3 per cent. Nine nucleated red cells were found in dog 849 which also exhibited anisocytosis, poikilocytosis, polychromatophilia, and target cells. No target cells were seen in the other dogs. Anisocytosis was found in one healthy dog, and polychromatophilia in 2 dogs. The serum-alcogel test was negative at 5 minute readings. Filaria (Dirofilaria immitis) have been observed in only one dog. In this connection it may be of interest to present the occurrence of filaria in 2 cases in another series of 24 dogs.

Table III exhibits comparative hematologic findings previous to and following splenectomy. In dog 844 these findings were from samples obtained 1 day before and prior to operation and on the 3rd and 19th postoperative days. In dog 814 a complete series of tests was run shortly before operation and up to the 31st day on 5 different postoperative days. Postoperatively dog 814 developed a secondary anemia which, however, on the 31st day appeared to have subsided. In this animal target cells and Howell-Jolly bodies were observed following splenectomy. In dog 844 no target cells were seen and Howell-Jolly bodies appeared in the control. Nucleated cells appeared only in this animal following operation. There is a trend of lymphopenia postopera-

TABLE II.—TWENTY COMPARISONS OF RED AND WHITE BLOOD CELLS OBTAINED FROM 16 HEALTHY DOGS

Dog number	Red blood cells in millions	Differential smear of red blood cells					White blood cells in thousands	Differential count of white blood cells					
		Nucleated cells	Anisocytosis	Poikilocytes	Polychromasia	Target cells		Non-segments	Segments	Lymphocytes	Monocytes	Eosinophils	Basophils
851	7.48	o	o	o	+	o	11.6	5	62	31	2	o	o
67	8.19	o	o	o	o	o	15.4	4	55	38	3	o	o
840	8.14	o	o	o	o	o	10.4	4	67	28	1	o	o
818	8.38	o	o	o	o	o	9.6	1	61	19	4	15	o
849	7.01	9	+	+	+	+	12.2	33	48	13	2	3	1
814	6.98	o	o	o	o	o	12.0	12	51	36	3	o	o
825	6.76	o	o	o	o	o	8.6	10	56	31	1	2	o
833	6.74	o	+	o	++	o	15.4	8	45	24	7	16	o
846	7.15	o	o	o	o	o	12.8	3	75	17	2	o	3
850	7.56	o	o	o	o	o	11.4	4	62	32	2	o	o
49	7.40	o	o	o	o	o	11.0	4	46	43	6	o	1
44	7.09	1	o	o	o	o	11.2	5	35	52	6	1	o
819	7.01	o	o	o	o	o	13.6	3	49	28	7	13	o
852 1. day	7.32	o	o	o	o	o	8.4	4	67	29	o	o	o
19. day	6.21	o	o	o	o	o	10.4	2	65	24	9	o	o
844 1. day	8.47	o	o	o	o	o	12.8	4	54	37	4	1	o
2. day	8.33	o	o	o	o	o	10.8	3	56	34	6	1	o
845 1. day	6.59	o	o	o	o	o	7.0	2	37	61	o	o	o
3. day	6.54	o	o	o	o	o	7.0	3	44	50	2	1	o
5. day	6.71	o	o	o	o	o	16.4	6	60	28	6	o	o

o=Negative + =Present ++ =Markedly increased

tively in dog 814. The platelet count does not alter and is within normal limits. The coagulation times of 100 per cent whole blood do not change significantly. The sedimentation rate is increased in dog 814 following operation and approaches its preoperative value on the 31st day. The clot retraction is present following operation in both dogs. On the 3rd and 4th postoperative days, however, there is a slight increase of the extracorpuscular volume of the clot. The only abnormal finding in both dogs postoperatively is the increased clot firmness. This increased clot firmness persists for several weeks and exhibits in dog 814 a gradual decrease which, however, is still well above the preoperative values on the 31st postoperative day.

Table IV exhibits a complete series of hematologic findings in 2 dogs with autotransplantation of the spleen to the femoral artery and vein and in 1 dog transplantation of the splenic vein to the middle colic vein. In all dogs there was a slight fall in red cell count, hemoglobin, and hematocrit. Howell-Jolly bodies were seen also in the controls of dog 67 and dog 846. Target cells could be observed in dogs 840 and 846, and nucleated red cells were seen in dog 67 following spleen transplantation. The sedimentation rate is increased on the 2nd and 4th postoperative days, whereas unchanged on the 1st postoperative day. The coagulation time of 100 per cent whole blood is within normal limits. The platelet count was unchanged throughout. Clot retraction was present in all instances. In dog 67 there was an increase of the clot volume, signifying decrease in serum volume and an increase of the extracorpuscular volume of the clot. In all instances there was a slight fall in lymphocytes postoperatively within the 1st and 4th

TABLE III.—COMPARATIVE HEMATOLOGIC FINDINGS IN 2 SPLENECTOMIZED DOGS

Test	Dog 844				Dog 814					
	Preoperative day		Postoperative day		Pre-operative day	Postoperative day				
	1	0	3	19	0	3	4	10	12	31
Red blood cells in millions	8.47	8.33	8.79	9.04	6.98		5.74	5.15	5.12	7.40
Hemoglobin in grams	17.2	17.0	17.0	15.5	14.0		11.5		10.0	13.5
Hematocrit, per cent	59	55	55	50	50	38	34	33	32	43
Sedimentation rate, 60 min., mm.	0	0	0	3	0	40	41	37	26	6
Alcogel test, 5 min., 37°C.		0	0	0	0		0			0
Coagulation time, 22°C., min.	2	2	4	5	3	4	5	7	7	5
Platelets in thousands	220	240	235	225	290	215	235	215	220	240
Clot retraction: Clot volume, per cent	64	59	74	59	62		65	47	36	51
Extracorpuscular volume, per cent	5	4	19	9	12		21	14	4	8
Clot firmness, mm. Hg	120	125	360	>500	65	>500	415	300	230	210
White blood cells in thousands	12.8	10.8	18.4	16.8	12.0	11.6	10.6	21.0	17.0	11.4
Differential count Nonsegments	4	3	11	8	10	33	26	18	2	17
Segments	54	56	58	41	51	48	51	60	57	43
Lymphocytes	37	34	27	43	36	13	15	15	28	32
Monocytes	4	6	3	8	3	2	5	7	4	8
Eosinophils	1	1	0	0	0	3	1	0	0	0
Basophils	0	0	1	0	0	1	2	0	0	0
Nucleated red blood cells	0	0	0	0	0	9	22	1	1	1
Howell-Jolly bodies	0	+	+	+	0	+	+	++	+	+
Microcytes	0	0	0	0	0	+	0	0	0	0
Anisocytosis	0	0	0	0	0	+	+	+	+	+
Macrocytes	0	0	0	0	0	+	+	0	0	0
Poikilocytes	0	0	0	+	0	+	+	+	0	0
Polychromasia	0	0	+	+	0	+++	+++	+	+	+
Target cells	0	0	0	0	0	+++	+++	+	0	+

0=Negative +=Present ++=Markedly increased +++=Excessive

day. The only spleen-transplanted animal which survived was dog 840 in which continued tests up to the 20th postoperative day were run. In all dogs the clot firmness was markedly increased following operation. This increase was more pronounced on the 2nd postoperative day than on the 1st postoperative day in dog 67. It showed in dog 840 a tendency to decrease, although on the 20th postoperative day it still was markedly increased.

It was customary in these studies to obtain platelet count, hematocrit and sedimentation rate values on the 1st postoperative day and to take blood for the complete series of tests on the 2nd postoperative day. Because of this practice, we were able to secure platelet counts from all dogs postoperatively. These counts are presented in Table V. As can be seen from this table, there is no change in platelet count in all dogs, no matter which operative procedure has been employed. Hematocrit and sedimentation rate values were also unchanged on the 1st postoperative day in dogs 845 and 849 which had a second spleen transplanted to their femoral artery and vein. In dog 814 there was also no change found in the sedimentation rate and in the hematocrit values on the 1st day after which splenectomy was carried out.

TABLE IV.—COMPARATIVE HEMATOLOGIC FINDINGS IN 2 DOGS WITH AUTOTRANSPLANTED SPLEEN AND IN 1 DOG WITH TRANSPLANTATION OF SPLENIC VEIN

Test	Autotransplantation of spleen							Transplantation of splenic vein	
	Dog 67			Dog 840				Dog 846	
	Preoperative day	Postoperative day		Preoperative day	Postoperative day			Preoperative day	Postoperative day
	0	1	2	0	4	10	20	0	1
Red blood cells in millions	8.19		7.26	8.14	7.07	6.16	6.05	7.15	6.49
Hemoglobin in grams	18.0		14.5	16.5	13.5	13.5	13.5	14.5	13.5
Hematocrit, per cent	44	40	44	54	44	42	44	48	41
Sedimentation rate, 60 min., mm.	0	0	38	0	38	37	9	8	2
Alcogel test, 5 min., 37°C.			0	0		0		0	0
Coagulation time, 22°C., min.	5	2	1.5	3	8.5	3	3	3	5
Platelets in thousands	230	200	220	230	194	240	230	220	210
Clot retraction: Clot volume, per cent	62	77	63	64	56	52	48	54	49
Extracorpuscular volume, per cent	18	37	19	10	12	10	4	6	8
Clot firmness, mm. Hg.	65	270	>500	85	>500	270	230	140	290
White blood cells in thousands	15.4		8.4	10.4	13.8	15.4	10.2	12.8	22.2
Differential count									
Nonsegments	4		50	4	28	7	4	3	19
Segments	55		23	67	46	46	41	75	71
Lymphocytes	38		24	28	16	41	53	17	9
Monocytes	3		3	1	10	6	1	2	1
Eosinophils	0		0	0	0	0	0	0	0
Basophils	0		0	0	0	0	0	3	0
Nucleated red blood cells	0		14	0	0	0	0	0	0
Howell-Jolly bodies	+		+	0	+	+	+	+	+
Microcytes	0		0	0	0	0	0	0	0
Anisocytosis	0		+	0	0	++	+	0	++
Macrocytes	0		0	0	0	0	0	0	0
Poikilocytes	0		+	0	0	++	0	0	+
Polychromasia	0		++	0	++	+	+	0	+
Target cells	0		0	0	0	+	0	0	+

0 = Negative + = Present ++ = Markedly increased

DISCUSSION

1. Hypersplenism. There are numerous reports and observations on splenomegaly in the literature in connection with various diseases of different nature signifying an enlarged spleen.

Ordinarily the spleen is only increased in conditions with splenomegaly, which, however, are not physiologic but the result of pathologic changes. In introducing a second spleen or several spleens, the part of the circulation to which the organ is connected may also be significant. It might well be that the normal site of the spleen in the circulatory system is of functional significance. In spleen transplantation there are considerable technical difficulties to overcome, and it is obvious that to certain parts of the circulation a spleen could not be attached.

The term "hypersplenism" has been used in the literature with various meanings, e.g., the presence of accessory spleens, "hyperactivity"

TABLE V.—PLATELET COUNTS FOLLOWING SPLENECTOMY, HOMOTRANSPLANTATION OF SECOND SPLEEN, TRANSPLANTATION OF SPLENIC VEIN AND AUTOTRANSPLANTATION OF SPLEEN IN DOGS

Dog			Operative procedure	Platelet count in thousands			
				Before operation		After operation	
Number	Sex	Weight, kgm.		Day	Count	Day	Count
844	Male	23	Splenectomy	0	240	3	235
						19	225
814	Male	21		0	290	1	280
						3	215
						4	235
						10	215
						12	220
						31	240
845	Female	19	Homotransplantation of second spleen	0	285	1	270
849	Male	18		0	300	1	345
846	Female	16	Transplantation of splenic vein to middle colic vein	0	220	1	210
818	Male	16	Autotransplantation of spleen	0	285	1	190
67	Male	20		0	230	1	200
						2	220
840	Female	15		0	230	4	194
						10	240
						20	230

of the spleen, or increased hemolytic spleen action. Nothing is known about the physiologic functions of the spleen in a "hyperactive" state. Singer, Miller, and Dameshek speculated that such hyperactivity may concern the "total" of splenic functions or "selectively" be limited to one function.

Accessory spleens are only detectable following laparotomy and careful search. It is not known whether their single or multiple occurrences amplify physiologic functions of the spleen whatever they may be. Curtis and Movitz reviewed recently the literature on accessory spleens in humans. Their own series of 178 patients represented an incidence of 31 per cent throughout various splenic disease and age groups. They made the observation that the unremoved accessory spleen may cause a recurrence of either primary thrombocytopenic purpura or congenital hemolytic icterus. Significant is their finding that persistent recovery from a recurrence after splenectomy was observed following the surgical removal of accessory spleens at a second operation in a case of congenital hemolytic icterus.

There is still another occurrence of multiple accessory "spleens" and as many as 400 have been counted in one single patient. They were found scattered throughout the peritoneal lining and were considered as transplants resulting from traumatic rupture of the spleen and seeding of the peritoneum with splenic fragments. They often developed subsequent to splenectomy for traumatic rupture of the spleen. Buchbinder and Lipkoff reviewed the literature of this condition for which they introduced the term "splenosis." The actual frequency of occurrence of splenosis is not known according to Curtis and Movitz. These authors stress the clinical significance of accidental production of splenosis during a splenectomy for primary splenic disease. It will have to be shown whether the experimental production of splenosis in normal nonsplenec-

tomized animals would result in certain increased physiologic splenic functions.

2. Spleen transplantation. The transplantation of the spleen has been attempted by several investigators. The usual approach was transplantation of autogenous and homologous spleen or spleen tissue without anastomosis of the splenic artery and splenic vein to the circulation. Such autotransplantations of splenic tissue were successful with some investigators (24). The other approach of transplanting the spleen to the circulatory system has been made by Carrel (6, 7), who employed his suture method for vessel anastomosis. Carrel (7) concluded that the section of the vessels of the spleen of a dog, "the section of their nerves, the suspension of their circulation for about 50 minutes and their extirpation and perfusion with Locke's solution do not modify their functions and their anatomical condition when they are replanted on the same animal." Our investigations, using the nonsuture method of Blakemore, Lord, and Stefko, have been successful inasmuch as one of the 4 dogs with autotransplants survived and was observed for 31 days. The 2 dogs in which a second spleen was transplanted lived for only 2 days.

The cause of the death of the 5 spleen-transplanted animals may be due either to bronchopneumonia, peritonitis, or to intrasplenic hemorrhage. It is not clear whether the animals hemorrhaged most of their blood into the transplanted spleen and that they died of hemorrhagic shock. The possibility exists that the spleen tumor may have compressed the aorta, vena cava, or other vital vessels or organs. All these giant spleens were signified by the presence of large quantities of blood. There can be no doubt that they originated from the influx of blood.

In one animal only splenomegaly and no other pathologic changes were observed at autopsy. At least in this animal, it appears to be certain that the cause of death was due to the enlarged spleen. Whether the hemorrhage into the spleen as such, or the sequelae due to the splenomegaly were primarily responsible for the death of the animals cannot be decided. It is quite possible that these animals died of shock following hemorrhage into the spleen.

In order to eliminate splenomegaly, the spleen of one animal was injected with adrenalin shortly following transplantation. This resulted in rather immediate contraction of the slightly enlarged spleen. It is of interest to note that apparently this one single adrenalin injection inhibited any future development of splenomegaly. This animal survived, and on exploratory laparotomy on the 26th postoperative day we observed a slight decrease in the size of the spleen from its original size previous to splenectomy, thus corroborating the palpatory findings obtained on any of the postoperative days previously. The phenomenon of splenomegaly as found on 5 occasions following autotransplantation of the spleen in 3 dogs or following homotransplantation in 2 dogs merits further study.

Loeb recently reviewed the literature on the interaction of the "individuality differentials" of host and transplant. He designates as individuality differential a particular characteristic which is common to all the various tissues, organs, and body fluids of an individual and distinguished it from another. Loeb finds that "transplantations by blood vessel anastomosis are of special interest because they make possible a separation of the effects of the body fluids on transplanted tissues from those of the host cells." Loeb summarized the observations of Carrel and of Guthrie who, in employing blood vessel anastomosis found that not only autotransplantation but also homotransplantation of kidney, thyroid, adrenal, and ovary, succeeded. It may well be that homotransplantation of organs can be successful only in using vessel anastomosis instead of simple grafting.

3. Hematologic observations. a. Control dogs. It is of interest to note the wide variation of red and white blood counts and in a few cases a marked eosinophilia. The only case of filariasis in dog 845 may have affected the differential count; however, this cannot be stated with certainty. There is also marked variation in hemoglobin and hematocrit values. Red cell sedimentation is either present or absent.

The coagulation times are within normal range. At the time these investigations were performed, the blood saline coagulation time

test of Copley and Houlihan (11) was not developed and changes in blood coagulability of healthy dogs could therefore not be correlated to any of the other hematologic findings. Meanwhile, such changes in coagulability have been shown in animals of various species (12).

The platelet count with the Copley-Robb method is well within normal range as established by these workers (14). It should be emphasized that stains in proper concentration should be employed in making the count. In the original paper of Copley and Robb (13, 14) a much lower concentration of brilliant cresyl blue stain was given. This employed stain had a higher dye content and was of foreign source. Meyer (25) found that with the originally recommended concentration of 0.2 per cent dye the platelets would not take the stain. We could corroborate his observations in employing brilliant cresyl blue N V-27. In making a 0.5 per cent concentration of this dye, we found satisfactory staining of platelets (9).

According to the method of Aggeler, Lucia, and Hamlin, the extracorpuscular volume in most cases showed only small values. The necessity for introducing the correction to the extracorpuscular volume has been discussed in the section of methods. These corrections were insignificant in all control dogs.

The clot firmness of Lalich and Copley (20) was in the majority of instances below 180 millimeters of mercury, viscometers of internal diameters of 10 millimeters in the wide portion and 3 millimeters in the narrow portion being used. Repeated tests on different days in the 3 dogs 852, 844, and 845 showed close agreement. In only 3 dogs the clot firmness in these tubes was 220 millimeters of mercury or more. This test is a measure of the hemostatic function of the blood and, except in hemophilia, has not yet found clinical application.

The alcogel reaction of serum was found negative in all dogs. This test belongs to the group of lability reactions and has been found not to occur in healthy humans. There is no correlation of this test to the sedimentation rate. The findings with the alcogel test in healthy dogs are the first to be reported.

The observed wide variations in data obtained with certain hematologic tests in different dogs or at times in the same animal on different days (see Table II, Dog 845) suggest that control values should preferably always be run in the same animal previous to operative procedures. This practice promises to better establish any hematologic changes brought about by surgical manipulations.

b. Splenectomized dogs. One splenectomized dog exhibited definitely secondary anemia. This phenomenon has been first observed in dogs by Pearce. The other dog showed only insignificant decrease in hemoglobin and hematocrit values on the 19th day. Such a trend of anemia may better have been brought about, in case more determinations would have been made. Any blood loss due to the operation was minimal and could not account for the anemia which developed in dog 814. The hematopoietic activity postoperatively in dog 814 runs parallel with the hemoglobin, red blood cells, and hematocrit values, and returns to approximately the preoperative values on the 31st day.

Singer, Miller, and Dameshek observed Howell-Jolly bodies as a constant finding in 19 human subjects who were splenectomized for various clinical conditions. Roth was the first to describe Howell-Jolly bodies after splenectomy in man. Red cells containing these bodies were observed by Jolly to occur normally in the blood of young mammals. We found them occasionally in adult dogs preoperatively (Tables III and IV). However, they were always present following splenectomy and spleen transplantation. Target cells were found by Singer and associates in most cases following splenectomy. We observed these cells in 1 splenectomized and 2 spleen-transplanted dogs.

The claim that the platelet count is increased following splenectomy has not been substantiated after splenectomy of normal dogs. The frequent occurrence of an increased platelet count following splenectomy in certain pathologic conditions with splenomegaly in humans is frequently misinterpreted to mean that any splenectomy even in healthy animals and humans is followed by an increase in the platelet count. There have been

several investigators who claimed that thrombocytosis occurred postoperatively in various surgical conditions. A discussion of these claims is given in a recent study by Adams. We cannot enter into a discussion of the controversy pertaining to postoperative thrombocytosis because we are only concerned here with the observations of thrombocytosis following splenectomy in healthy animals.

The effect of splenectomy on the platelet count was summarized by Krumbhaar. He states that the rise in platelet count following splenectomy was found both experimentally and clinically, though the evidence varies as to the duration and cause of the increase. In Krumbhaar's own experiments on dogs he found increased counts from 50 to 200 per cent higher after 3 to 12 months at the end of the observation than before operation. Immediately following the operation there was a considerable rise, but after a drop toward normal, a second rise was observed which was lasting. He speculates that the postsplenectomy thrombocytosis is the result of both decreased thrombocytolysis and decreased inhibition of platelet formation. It should be noted that Loesch, Witts, and Zimmermann made several studies of platelet counts before and after operation in 3 dogs. In 2 dogs they ligated the splenic veins and they splenectomized a third dog. There are marked fluctuations in their platelet counts.

In our experiences, we have found at times great fluctuations in platelet counts in healthy dogs on various days, i.e. increases up to 91 per cent, otherwise the values were usually constant over a long period of time. It is not understood to what mechanisms such fluctuations are due. One may find similar objections if one analyzes the detailed data of other workers who have made platelet counts in experimental animals or in healthy humans. Although it is not possible for us to discuss the literature on platelet counts, we wish to emphasize that platelet counts should be well controlled. In our appraisal there are few reliable methods for making platelet counts. Thus perhaps most papers giving values for them rather confuse the actual facts and do not contribute to a better understanding of the number of platelets in the circulating blood.

Wollstein and Kreidel reported platelet counts in children on whom splenectomy was performed. They found that in 3 cases of traumatic rupture of the spleen, in 20 cases of rheumatic disease, and in 4 cases of congenital, hemolytic icterus, there was no immediate increase after the operation, but an increase appeared toward the middle or end of the first week. Shore and Kreidel reviewed the literature on 210 unselected surgical cases exclusive of splenectomies by 3 groups of observers. A marked rise of platelets was manifested from the sixth to the fourteenth postoperative day. However, "a similar rise was found in 3 traumatic cases without operation." Wollstein and Kreidel did not find "any appreciable rise in the platelet count" in 4 children following operations other than splenectomy.

We do not need to question the results of platelet counts so consistently obtained in certain clinical conditions in man with splenomegaly which have shown marked decreases in the count previous to operation and a return to normal limits following splenectomy. We believe platelet count increase is true only in such pathologic conditions and that the increase in platelet counts postoperatively following the removal of the spleen in healthy subjects will still have to be proved. Binet and Kaplan did splenectomies in 3 dogs. Platelet counts before and after operation were the same in one dog, slightly decreased in a second dog, and moderately increased in a third dog following splenectomy. Platelet counts can be very demonstrative, although they should be reliably recorded with improved methods of counting the platelets.

The occurrence of accessory spleens should be considered in studying the effect of splenectomy on the platelet count. To our knowledge, no importance has been placed on this phase of the problem. Such accessory spleens may substitute for any deficiency following the removal of the spleen. We often found in autopsies and during laparotomies accessory spleens in dogs; however, none was observed in our 2 splenectomized animals.

c. Spleen transplanted dogs. The comparative series of hematologic tests which were completed in 3 dogs show similar results as

obtained in dogs following splenectomy. There is a decrease in red cell count, hematocrit, and hemoglobin in dogs 67 and 840. The occurrence of Howell-Jolly bodies and target cells have been discussed in the preceding section. Findings on the first postoperative day in dog 846 with anastomosis of the splenic vein to the middle colic vein suggest a trend toward anemia. In all instances there is a trend of lymphopenia within 4 days postoperatively. This was also indicated in the splenectomized animals. It is of interest that the sedimentation rate does not increase before the second postoperative day, a finding which we also observed in the 2 dogs in which a second spleen was transplanted. In these homotransplanted dogs, there was no change in the sedimentation rate on the first postoperative day. No tests could be made on the second postoperative day because the dogs had died.

A comparison of the platelet counts showed no significant change in any of the 6 spleen transplants. These findings are of additional interest since 3 dogs (846, 818, and 67) exhibited splenomegaly already on the first postoperative day. The presence of extremely enlarged spleens together with normal platelet counts would indicate that splenomegaly *per se* is not always associated with a decrease in the platelet count. It seems to us that possibly specific pathologic conditions in certain diseases with splenomegaly account for the decrease in the number of platelets in the circulating blood. It is possible that this decrease of circulating platelets originates with pathologic changes of the enlarged spleen.

Our 5 cases with experimentally produced splenomegaly were apparently due to hemorrhage into the spleen. It is not known yet whether these giant spleens developed so rapidly due to blockage of the venous return or other disturbances.

d. Observations on clot firmness. There are no other striking differences in the results obtained with various hematologic tests following operation, with the exception of the clot firmness test. The clot firmness was increased in all instances of spleen transplantation and showed similar findings as in the 2 splenectomized dogs. This interesting observation, however, is not specific to severance of or injury to the splenic vessels, but has been observed in 3 other dogs following laparotomies. Whether the animal has the ability to increase the hemostatic function of the blood following abdominal or other major operation, as indicated by these increased clot firmness values, should be kept open for further investigation.

The mechanism of clot firmness is not as yet understood. There is no correlation between clot retraction and clot firmness, as has been shown in model tests by Copley (10). These observations amplify the findings of Lalich and Copley (20) who found decreased or absent clot firmness with hemophilic blood. It is well known that blood coagula from hemophilic patients exhibit syneresis. The clot firmness test may prove to be a valuable clinical aid for estimating the hemostatic function of the blood. Moreover, it invites a study whether patients with certain hemorrhagic disorders would also show an increase in clot firmness following splenectomy or other operations and whether the deficiency of a certain substance or substances would account for the impaired hemostatic function of the blood. Hemostasis is not identical with blood clotting (15, 21, 27). The latter only comprises the different processes which lead to the clotting of blood *in vivo*. Arrest of hemorrhage or hemostasis depends upon other factors which reside both in the blood and the site of the traumatized tissue or the damaged blood vessels.

SUMMARY

1. Twenty series of comparative hematologic tests have been made in 16 healthy mongrel dogs. Each series consisted of red blood count, and its differential smear, hemoglobin, hematocrit, total and differential white blood count, platelet count, sedimentation rate, serum alcogel, differential clot retraction, coagulation time of 100 per cent native blood, clot firmness, and search for filaria. Data obtained with these series of tests are presented and discussed.

2. Eight animals were subjected to the following operative procedures: (a) splenectomy, (b) reimplantation of the animal's spleen to a different part of the circulation, and (c) implantation of a second spleen to the general circulation.

3. Two dogs were splenectomized and complete series of hematologic findings were obtained preoperatively and on different days postoperatively.

4. In 3 dogs autotransplants of the spleen were made to the femoral artery and femoral vein by means of the nonsuture method with vitallium tubes. In 1 animal the splenic vein was transplanted to the middle colic vein. In 2 dogs a second spleen was transplanted to the femoral artery and femoral vein. The operative procedures are presented.

5. Two dogs died with peritonitis on the second postoperative day following homotransplantations of a second spleen. Three animals with autotransplants of the spleen died on the second postoperative day. They all exhibited splenomegaly and each spleen had a weight of about 500 grams. Two animals with autotransplants had one-sided pneumonia, whereas a third animal did not exhibit any pathologic changes other than the splenomegaly. It is believed that all 3 of the dogs died of hemorrhage into the transplanted spleen.

6. One dog with autotransplantation of the spleen survived. The spleen substance of this dog was injected with adrenaline hydrochloride at the time of the completed anastomosis. No splenomegaly developed in this animal. On exploratory laparotomy on the 27th day, the spleen was about two-thirds of its original size. Good pulsation of the splenic artery throughout the anastomosis and good venous return of the femoral vein were found. It is not clear whether the one single injection of adrenalin was responsible to counteract the development of splenomegaly and whether its absence permitted the survival of the animal.

7. Complete series of hematologic findings are presented from 2 dogs following autotransplantation of the spleen and anastomosis of the splenic vein to the middle colic vein. The hematologic findings are similar to those which were obtained in the two splenectomized animals.

8. Clot firmness which signifies increased hemostatic function of the blood was always found increased following operation. This phenomenon was a constant finding following laparotomy in 3 other abdominal operations in dogs, and is not considered to be in direct connection with the spleen function.

9. Platelet counts have been obtained preoperatively and postoperatively in 2 dogs with homotransplants of a second spleen, and in the 4 dogs with autotransplants of the spleen. No significant change in the platelet count was observed in the peripheral blood of these animals as also was the case in the two splenectomized dogs. It is emphasized that splenomegaly *per se* may not affect the platelet count.

10. The principle of introducing one or multiple spleens into various parts of the circulation is discussed as a method to advance our knowledge of the functions of the spleen. The direct attachment of a second spleen to the circulatory system is proposed as a method for increasing physiologically active splenic tissue.

11. Hypersplenism with regard to its various designations and the significance of accessory spleens are discussed.

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EDITORIAL

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THE CHEMOTHERAPY OF CANCER

AFTER long desire a beginning has been made recently in the chemical treatment of advanced cancer, and, in fact, results of no small magnitude have been achieved since 1941. The desire to solve a problem, in itself, is insufficient to do it; in good science the problem must be conceived clearly and the simplest possible approach devised, bearing in mind that the greater the number of variables the greater the number of equations are required. The advances in medicine are directly related to the development of the other sciences which in our age has been stupendous.

It is now possible to see practical methods of approach to the difficult problem of disseminated cancer, and the concepts seem to be easier to define than they were a decade ago. Several inhibiting agents have been found which are more or less effective in the treatment of the tumors of man and animals. The advances have concerned a few specific tumors rather than cancer as a whole, and here the development resembles the history of treatment of infectious diseases; cure of infection did not evolve as such but over the years treatments were gradually devised for specific and particular infectious diseases.

Work with pure chemicals has been the most profitable; crude extracts and laboratory soups have yielded only slight dividends. Such a great number of pure compounds are available for systematic investigation that the chance of success from an erratic procedure empirically developed is too small to interest most professional investigators. In studying normal structures, one is also contributing to the foundation of the study of cancer; the systematic investigation of disease is possible only in proportion to what is known about the function of normal organs.

No doubt the greatest handicap in the development of cancer treatments has been the lack of things to measure; time is of the essence in the evaluation of putative therapeutic modifications and cancer is frequently so indolent and diffuse as to defy quick and precise measurement. Always one is faced with the fear that a little improvement may escape detection and a valuable lead thus be overlooked. The only rapid indicators of neoplastic activity now available in man concern tumors of the blood-forming organs and cancer of the prostate. In neoplasms of hemopoietic tissue, the circulating cellular elements are available for quantitative study and in prostatic cancer the serum phosphatases[1,2] provide rapid and

[1]GUTMAN, A. B., and GUTMAN, E. B. J. Clin. Invest., 1938, 17: 473.
[2]HUGGINS, C., and HODGES, C. V. Cancer Res. 1941, 1: 293.

elegant indices of the activity of the cancer. Obviously the development of a chemical method for the study of the activity of any other cancer will be of first class importance.

At this time it is only possible to notice those chemical methods of treatment which seem to have been well established. They may be divided into 3 groups according to their action.

1. Necrotizing agents. It has long been known that certain bacterial products when administered parenterally to creatures bearing sarcomas produce severe hemorrhage in the tumors within a few hours with subsequent necrosis of the affected area of the neoplasm. The separation of the hemorrhage producing agent in a culture of Serratia marcescens (Bacillus prodigiosus) from toxic and inert contaminates has been accomplished by Shear and co-workers in a brilliant series of investigations[3,4]; it has been found to be a polysaccharide which is active in very small amount. Unfortunately, in most cases the necrosis of the tumor is not complete and while certain tumors regress, some of the tumor usually remains viable. From experiences with other agents, it is not considered necessary nor desirable that an anticancerous agent produce instant and massive necrosis to be effective.

2. Competitive inhibition and the essential foodstuffs. It has been found in cancer of the prostate that androgen is often an essential item for the nutrition of the malignant cell; the tumors grow vigorously when androgen is administered in appropriate dosage and the cells tend to wither when the androgen supply is removed (orchiectomy) or estrogen is administered. Estrogen was the first agent of known chemical composition, aside from radioactive chemicals, which ameliorated widespread cancer and was the first substance known which affected cancer adversely when fed by mouth. Both estrogen and orchiectomy are in effect chemotherapeutic agents although nonspecific ones.

Heilman and Kendall[5] found that the compound E of Kendall derived from the adrenal cortex caused massive involution of lymphosarcomas in female and young male mice. The work of Abraham White and Dougherty[6] has demonstrated a relationship of the adrenal cortex to lymphocytes in that adrenal stimulation causes a decreased activity of lymphoid tissue. The damaging effects of 11-dehydro-17-hydroxycorticosterone on lymphoma is in line with these biochemical observations.

The theory of competitive inhibition arose from the work of Wood and Fildes wherein sulfonamides in proper concentrations were found to eliminate the effectiveness of *p*-aminobenzoic acid, a substance essential for the growth of certain bacteria.

3. Nuclear damage. It has long been established that irradiation damages cells, and because of the frequency of induced mutations as well as much other evidence, the principal effect of irradiation is believed to be on the nucleic acids of the cell nucleus. The radioactive isotopes with a short period of decay constitute a useful method of presenting soluble radioactive chemicals to the organism as a whole. Radioactive phosphorus has great value in chronic lymphatic and myelogenous leukemias[7] and is probably the best therapeutic agent which is now available for polycythemia vera.[8]

The nitrogen mustards (β-chloroethyl amines) have presented an interesting devel-

[3]Shear, M. J., and Andervont, H. B. Proc. Soc. Exp. Biol., N. Y., 1936, 34: 323.
[4]Hartwell, J. L., Shear, M. J., and Adams, Jr., J. R. J. Nat. Cancer Inst., 1943, 4: 107.
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opment in the cancer problem. Following the demonstration of Lushbaugh that these chemicals caused a lowering of the lymphocyte count of rabbits, they have been studied systematically from a biochemical standpoint.[9] The nitrogen mustards have been used in clinical patients in the treatment of Hodgkin's disease, and it has been found that regression[10, 11] sometimes occurs after their use. The mustards are the only agents known which can produce mutations chemically,[12] an effect which hitherto has only been produced by radiant energy

[9]Gilman, A. and Philips, F. S. Science, 1946, 103: 409.
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Still another agent capable of producing regressions in cancer is ethyl carbamate (urethane) which has produced regression of transplantable carcinoma in mice[13] as well as in human leukemia.[14] Urethane has long been known to delay cell division[15] without great interference with respiration, but the present interest in this substance in cancer research is due to the efforts of Haddow. It has recently been shown that urethane is able to reduce the growth of human prostatic cancer[16] and notably in patients where a relapse has occurred after hormonal treatment with orchiectomy and estrogen; the drug is not antiandrogenic and so constitutes a new principle in the treatment of advanced prostatic cancer acting by pycnosis. The drug is toxic and great care must be exercised in its administration; however, it is another shot in the therapeutic locker.

Charles Huggins.

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THE BOOK SHELF

MEDICAL ASPECTS OF THE LEWIS AND CLARK EXPEDITION (1804–1806)

O. LARSELL, Portland, Oregon

THE Lewis and Clark Expedition (1804–1806), sent by President Thomas Jefferson to the Columbia River, has had so important an effect on the subsequent history of the Pacific Northwest that all aspects of this epochal journey are of great interest. As leader of the Expedition, President Jefferson selected Captain Meriwether Lewis (1774–1809), of the United States Infantry. Lewis was an educated man with unusual qualities of leadership, and had been Jefferson's private secretary. He asked that William Clark (1770–1838), a 2nd lieutenant in the United States Artillery and a brother of George Rogers Clark, the well known Indian fighter, be appointed co-leader. Both men were born near Charlottesville, Virginia. Clark served as equal to Lewis in command of the Expedition and the leaders are referred to as Captains Lewis and Clark in historical records. Clark was a frontiersman and soldier of much experience and contributed greatly to the success of the venture. No regular physician was provided, but Lewis had sufficient medical knowledge to treat many of the ills of his company and Clark knew the simple medical practices of frontier life.

After collecting the necessary supplies and selecting a personnel of 27 men, the captains placed the Expedition into winter quarters at River du Bois, near St. Louis, late in 1803. Rigorous training during the winter fitted the men for the anticipated hardships of the journey. The party, with 15 or 16 additional men[1] who were to go only part of the way, started up the Missouri River in three boats on May 14, 1804. Its instructions were to make a geographical exploration of the country they were to traverse and to gather information about its natural history and the Indian tribes.

Lewis wrote to President Jefferson on May 29, 1803, as follows:

"Dr. Rush has favored me with some abstract queries under the several heads of *Physical History, Medicine, morals* and *religion of the Indians*, which I have no doubt will be serviceable in directing my inquiries among that people. Drs. Barton and Wister have each promised to contribute in like manner anything, which may suggest itself to them as being of any importance in furthering the objects of this expedition."[2]

The physicians to whom Lewis refers were Dr. Benjamin Rush (1745–1813), Dr. Benjamin Smith Barton (1766–1815), and Dr. Caspar Wistar (1760–1818), all of Philadelphia. Dr. Rush was the outstanding American physician of that day and was professor of the institutes and theory and practice of medicine in the University of Pennsylvania. Dr. Barton[3] was professor of natural history and botany, succeeding to Dr. Rush's chair at the death of the latter in 1813. He had become greatly interested in the Indians as a young man and was an authority on the subject. Dr. Wistar was professor of anatomy in the university and wrote the first American textbook on anatomy.

To aid in obtaining information about the Indians, the following list of queries resulted, as recorded by Captain Clark under the heading of "Physical History and Medicine":[4]

"What is their State of Life as to longivity?
"at what age do both sexes usually marry?
"How long do the Woman usually succle their Children?
"What is the diet of their Children after they wean them?
"Is polygamy admited among them?

From the University of Oregon Medical School.

Extracts from a book by the author, entitled *The Doctor in Oregon*, now in press.

[1]Clark, Charles G. Oregon Historical Quarterly, 1944, 45: 289–305.

[2]Original Journals of the Lewis and Clark Expedition, 1804–1806. Thwaites ed. New York: Dodd, Mead and Co., 1905, 7: 224.

[3]Middleton, William S. Ann. M. History, 1936, 8: 477–491.

[4]Lewis and Clark Expedition, 7: 283.

"What is the State of the pulse in both Sexes, Children, grown persons, and in old age, by feeling the Pulse Morning, Noon & Night & c.?
"What is their most general diet, manner of cooking, time and manner of eating; and how do they preserve their provisions?
"What time do they usually consume in Sleep?
"What are their *acute* diseases?
"Is rheumatism, Pluricy or *bilious fevers* known among them? & does the latter ever terminate in a vomiting of *black matter?*
"What are their chronic diseases—are palsy, apoplexy, Epilepsy, Madness, the goitre (or Swelled Neck) and the Venereal disease known among them?
"What is their mode of treating the *Smallpox* particularly?
"Have they any other disease amongst them, and what are they?
"What are their remidies for their different diseases?
"Are artificial discharges of blood used among them?
"In what manner do they generally induce evacuation?
"Do they ever use Voluntary fasting?
"What is the nature of their baths, and at what time of day do they generally use them?
"at what age do their women begin and cease to menstruate?"

In addition to preparing for his inquiries among the Indians, Lewis made provision against illness in his own party. In 1803 he estimated that the expense of the expedition would be $2500, of which $55 was for medicines and packing. He drew up a list of items needed as medical supplies. The items actually purchased represent some modification of the original list and are indicated in the following statement:[5]

"Bill of Gillaspy & Strong for Medicine
"Israel Wheelen Purveyor Bought of Gillaspy & Strong the following articles for the use of M. Lewis Esquire on his tour up the Missisipi River, & Supplied by his Order:—Viz.

"15 lb. Pulv. Cort. Peru	$30.00	¼ lb. Bals. Traumat.	.50
½ lb. Pulv. Jalap	.67	2 oz. Magnesia	.20
½ lb. Pulv. Rhei (Rhubarb)	1.	4 oz. Laudanum	.50
4 oz. Pulv. Ipecacuan	1.25	2 lb. Ung. Basilic Flav. 50	1.00
2 lb. Pulv. Crem. Tart	.67	1 lb. Ung. elap Calimin 50	.50
2 oz. Gum Camphor	.40	1 lb. Ung. Epispastric	1.
1 lb. Gum Assafoetid	.67	1 lb. Ung. Mercuriale	1.25
½ lb. Gum Opii Turk opt	2.50	1. Emplast. Diach S.	.50
¼ lb. Gum Tragacanth	.37	1. Set Pocket Inst.[a] small	9.50
6 lb. Sal Glauber	.60	1. Set Teeth Inst.[a] small	2.25
2 lb. Sal Nitri 33⅓.	.67	1. Clyster Syringe	2.75
2 lb. Sal Copperas	.10	4. Penis do	1.
6 oz. Sacchar. Saturn opt	.37	3. Best Laucets .80.	2.40
4 oz. Calomel	.75	1. Tourniquet	3.50
1 oz. Tartar Emetic.	.10	2. oz. Patent Lint	.25
4 oz. Vitriol Alb	.12	50. doz. Bilious Pills to Order of B. Rush 10	5.00
½ lb. Columbo Rad.	1.	6. Tin Canisters 25.	1.50
¼ lb. Elix. Vitriol.	.25	3. 8 oz. G.[d] Stop.[d] bottles 40	1.20
¼ lb. Ess. Menth. pip	.50	5. 4 oz. Tinctures do	1.85
¼ lb. Bals. Copaiboe	.37	6. 4 oz. Salt M.°	2.22
		1. Walnut Chest	4.50
		1. Pine do	1.20
		Porterage	.30
			$90.69"

[5]Lewis and Clark Expedition, 7: 236.

The total bill was somewhat in excess of the original estimate. While in St. Louis the Expedition was supplied by Dr. Antoine Francois Saugrain with additional packages of medicines, a home-made thermometer, and some experimental lucifer matches. Saugrain was a pioneer among the scientists of the Ohio and Mississippi Valleys, with hobbies of chemistry and electricity.[6] He no doubt attracted Meriwether Lewis, especially, who was near him from December 12, 1803, to May 20, 1804, the party having started nearly a week before Lewis himself left St. Louis. Very likely Lewis added considerably to his own stock of medical knowledge from contact with the doctor.

At the beginning of their travel up the Missouri River the men were in fine condition. In the early part of the journey there is but little mention of medical matters, but on July 23, Clark wrote in his journal[7] that one man had a tumor on his breast, which he later opened. A week later several of the men had bad boils. Near the present site of Dakota City, Nebraska, on August 14, Clark makes mention of a village of Indians which had been wiped out by smallpox 4 years earlier, stating that the huts had been burned and the wives and children had been put to death "with a view of them all going to a better country."[8] Four days later, near the present site of Sioux City, Iowa, he wrote: "Serjeant Floyd is taken verry bad all at once with Biliose Chorlick we attempt to relieve him without success as yet." The patient died on the 20th "with a great deal of Composure."[9] This was the only death suffered by the party during the entire expedition. On August 22, there is the item that the men had been troubled with stomach disorders, since leaving the Sioux River, from using water of the Missouri River on which floated a scum of mineral matter from a bluff upstream. According to Clark this scum contained alum, copperas, cobalt and pyrites. Lewis took a "Dost of Salts" to work off the effects of tasting some of the rock from which the material came.

The fall of 1804 found the party at the site of Bismarck, North Dakota, where it prepared to winter among the Mandan Indians. Clark's journal contains a notation, dated October 22, stating: "last night at 1 oClock I was violently and Sud-

[6]E. S. Meany, Washington Hist. Quart., 1931, 22: 295–311.
[7]Lewis and Clark Expedition, 1: 89.
[8]Lewis and Clark Expedition, 1: 110.
[9]Lewis and Clark Expedition, 1: 114.

denly attacked with the Rhumetism in the neck [probably spasmodic torticollis] which was So violent I could not move. Capt. [Lewis] applied a hot Stone raped in flannel, which gave me some temporey ease."[10] Clark suffered from this attack for several days and on the 25th he adds: "R. Fields with Rhumitism in his neck, P. Crusat with the Same complaint in his Legs—the party other wise is well, as to myself I feel but slight Simptoms of that disorder at this time."[11]

A more serious problem, however, soon confronted the leaders, namely, venereal infection of the men from the Mandan women. This involved diplomacy in dealing with the Indians as well as medical treatment and discipline of the men, who were ordered not to touch the wife of any Indian. The orders apparently were disobeyed, or unmarried squaws were available, and on January 14 (1805), Clark writes of sending Sergeant Pryor and five men, with some Indians, to hunt several men who had become infected. On the 21st he writes: "One man verry bad with the pox."[12]

On November 29, 1804, there is a brief note: "Sergeant Pryor in takeing down the mast put his Sholder out of Place, we made four trials before we replaced it."[13] Cold weather also brought frostbite to several of the men and on January 26 Clark wrote: "one man taken violently Bad with the Plurisie, Bleed & apply those remedies Common to that disorder."[14]

On February 11, 1805, Sacajawea, one of the wives of Toussaint Charbonneau, an interpreter engaged by the captains at the winter camp, "was delivered of a fine boy."[15] Charbonneau had two other wives among the Mandans but only Sacajawea accompanied him with the Expedition when it resumed its journey. This Shoshone girl, who was the only woman with the Expedition, had been purchased by Charbonneau from Indians who had taken her captive from her tribe as a little girl. She played a rôle in the later history of the Expedition by gaining a friendly reception for the half-starved party when it reached her own country of the Shoshone Indians, in southwestern Montana. The boy born at Mandan was Sacajawea's first child and the labor was tedious and painful. Clark continued:

"Mr. Jessome informed me that he had freequently administered a small portion of the rattle of the rattle-snake, which he assured me had never failed to produce the desired effect, that of hastening the birth of the child; having the rattle of a snake by me I gave it to him and he administered two rings of it to the woman broken in small pieces with the fingers and added to a small quantity of water. Whether this medicine was truly the cause or not I shall not undertake to determine, but I was informed that she had not taken it more than ten minutes before she brought forth; perhaps this remedy may be worthy of future experiments, but I must confess that I want faith as to it's efficacy."[16]

The last item of medical interest noted by Clark at the Mandan village bears the date of February 15. He wrote:

"one Chief of the Mandans returned from Capt. Lewises Party nearly blind, this Complaint is as I am informed Common at this Season of the year and caused by the reflection of the Sun on the ice & Snow, it is cured by jentilley swetting the part affected, by throwing Snow on a hot Stone."[17]

The journey up the Missouri was resumed on April 7, 1805, but little of medical interest is recorded. On May 14, while on the Yellowstone River, one of the boats which contained the medical supplies was swamped.[18] Much of the material was damaged and some was destroyed. Between Maria's River and the Great Falls of the Missouri, on June 10, Sacajawea fell ill. Clark wrote: "I blead her."[19] Four days later Clark noted:

"the Indian woman complaining all night & excessively bad this morning. her case is somewhat dangerous. two Men with the Toothake, 2 with Tumers & one man with a Tumer & a slight fever."[20]

On June 16 Lewis wrote in his journal concerning Sacajawea, who had not yet recovered, that two doses of barks and opium had slowed and strengthened her pulse and made it more regular. He had found it almost imperceptible, or very fast and irregular when it could be felt. There also was twitching of the fingers and of the "leaders" of the arm. In addition to "barks" and opium, Clark prescribed mineral water for her. The pulse improved, the twitching was reduced and a gentle perspiration came on, with much relief from pain. The woman complained chiefly of distress in the lower abdomen, Clark ascribing it to "an obstruction of the mensis in consequence of taking could."[21] He continued treatment with barks and laudanum.

The party reached Sacajawea's people in the middle of the summer of 1805, its food supplies exhausted, and in serious straits because of this and the scarcity of game. The Shoshone chief proved to be Sacajawea's brother, and a touching story of

[10]Lewis and Clark Expedition, 1: 202.
[11]Lewis and Clark Expedition, 1: 206.
[12]Lewis and Clark Expedition, 1: 250.
[13]Lewis and Clark Expedition, 1: 229.
[14]Lewis and Clark Expedition, 1: 251.
[15]Lewis and Clark Expedition, 1: 257.
[16]Lewis and Clark Expedition, 1: 258.
[17]Lewis and Clark Expedition, 1: 262.
[18]Lewis and Clark Expedition, 2:37.
[19]Lewis and Clark Expedition, 2: 141.
[20]Lewis and Clark Expedition, 2: 159.
[21]Lewis and Clark Expedition, 2: 164.

the reunion is related. The half-starved explorers were supplied with the provisions enough to meet their immediate needs from the Shoshone's own meager store, and the expedition, which had found itself in an almost desperate situation, was enabled to continue its journey.

The party pushed westward through the Rocky Mountains in September. Food was scarce, due to the lack of game, which was limited to a few pheasants and squirrels. Fish and roots formed a large part of the diet. The going became more and more difficult and the men became weak and debilitated, many suffering from dysentery and skin eruptions. Finally they were obliged to kill a colt for food.

On September 21 Clark wrote: "I am very sick today and puke which relive me."[22] On the 24th he continued: "Capt. Lewis sick all Complain of a *Lax* & heaviness at the stomack. I gave rushes Pills to several," eight or more of the men also being ill. On the following day he wrote that Lewis was very sick, and most of the party was complaining. He gave them salts and tartar emetic. He added, "Several men So unwell that they were compelled to lie on the Side of the road for Some time, others obliged to be put on horses. I gave rushes Pills to the Sick this evening."[23] Several deer were killed on September 30 and the condition of the men immediately improved with better food. However, in a few days the party was obliged to return to dried salmon and roots, with renewed gastrointestinal disorders. Not until they reached the Columbia, near the junction of the Snake River, on October 16, were they able to obtain fresh meat, in the form of "some nice fat dogs" which they purchased from the Indians. Everyone's health immediately improved. One of the leaders notes that he came to like the meat of "nice fat puppies."

While in western Montana, Lewis wrote that he tried to learn if the Shoshones had venereal disease among them, and to find out their remedies. Through the interpreter and his wife he was informed that sometimes they were affected, but he was unable to learn of any remedy they employed. "They most usually died of its effects." The captain thought that, because of the isolation of this tribe, both gonorrhea and syphilis must be native to America although he recognized that smallpox, from which the Shoshones as well as most of the other tribes had suffered severely, was an imported disease. He also made some observations regarding standards of sexual morality, stating that "some of their women appear to be held more sacred than in any nation we have seen." However, this was but comparative, and control appeared to be entirely in the hands of the husband, who for a suitable reward would barter his wife "for a night or longer."

With reference to childbirth among the natives, Lewis comments on the ease of delivery when the father was an Indian. He notes that when one of the Shoshone Indian women who had been helping the party transport its baggage had halted at a little stream, he inquired of the chief as to the reason. The latter informed him that the woman had stopped to deliver her fourth child and would soon overtake the party. This she did in about an hour, with her newborn babe, apparently as well as ever.

Clark wrote on October 17, 1805, of the numerous cases of sore eyes which he encountered among the natives, not only in the region of Kennewick, Washington, where the party then was, but among the Flatheads on the Kooskooske and Lewis Rivers which they had left some time earlier. Many of the Indians were blind in one or both eyes. Many of the natives also had lost their teeth at middle age, and in others the teeth were worn to the gums, especially in the upper jaw. He ascribed the bad teeth, in part, to the habit among the Indians of eating the "rine & scales" of the dried salmon, which constituted a large item of their diet, along with the flesh, and to sand attached to the edible roots which supplemented the salmon.[24]

On November 15, 1805, the Expedition arrived at the mouth of the Columbia River after travelling 4134 miles, according to Lewis's estimate.[25] Alexander MacKenzie had reached the western ocean through Canada in 1793, but Lewis and Clark were the first explorers to reach the Pacific by crossing the continent between the Canadian boundary and Mexico. Valuable observations and collections had been made and Indian tribes never before seen by the white man had been encountered. After crossing to the south side of the river they built winter quarters at Fort Clatsop, south of the present city of Astoria. The party reached the mouth of the Columbia at the worst part of the rainy season and was faced with a good deal of discomfort until quarters could be completed. Dated December 11 we find this entry: "rained all last night moderately. We are all employed putting up huts or Cabins for our winter quarters."[26] Several of the men were beginning to suf-

[22]Lewis and Clark Expedition, 3: 82.
[23]Lewis and Clark Expedition, 3: 86, 87, 88.
[24]Lewis and Clark Expedition, 3: 126.
[25]Elliott Coues, ed., History of Lewis and Clark Expedition (1893), 6: 74.
[26]Lewis and Clark Expedition, Thwaites ed., 3: 277.

fer from the excessive dampness; four of them had violent colds, one had dysentery, a third had tumors on his legs, and two had been injured by dislocations and strains.

Here again the problem of food obtruded itself. The Indians, who had learned to barter with the Boston ships and other fur traders, demanded high prices for everything they sold. On December 3 an elk was brought in, providing a much needed change of diet. Seven more elk were killed shortly afterward, but because of unusually warm weather much of the meat spoiled and the party had to resort to pounded fish again, resulting in the usual dysentery and weakness. On December 30 four more elk were shot, but the animals became scarcer as colder weather came on so that dog meat, blubber from a stranded whale, roots and berries served as food for a time. The captains remark that the men had acquired a taste for the flesh of dogs and that while living on it they were in better condition and health than at any time since leaving the buffalo country. In the early spring the annual run of the smelt or eulachon into the rivers from the ocean brought a welcome change of diet in great abundance. From this time on the food supply appears to have been adequate, both for the short remaining time at Fort Clatsop and on the journey eastward. A salt cairn, for the purpose of obtaining salt from sea water, had been built by the party at the site of the present town of Seaside, Oregon, some miles from Fort Clatsop.

There is also complaint about the incessant rain and the innumerable fleas. The Indians and their lodges abounded with these vermin which could not be kept out of the crowded quarters of the party. Other discomforts are mentioned by Clark as follows: "Sergeant Pryor unwell from dislocation of the shoulder, Gibson with the dysentery, Jo Fields with biles on his legs and Werner with a strained knee."

The sexual standards of the women of the Chinook tribe were unusually lax and venereal disease, already introduced by sailors of the fur-trading ships, is frequently mentioned. While on a short journey on November 18, Clark encountered some Chinook Indians and noted that he saw four women and some children covered with sores, scabs and ulcers, which he regarded as due to venereal disease. The Clatsop Indians also were commented on. The young women, many of whom were handsome, sought the men of the exploring party, apparently with the approbation of their friends and relatives. To save the party's supply of knives and other more valuable articles, the captains divided some ribbon among the men of the party "to bestow on their favorite lassies." Several of the men soon became infected with venereal disease. They were treated with mercury, some to the point of salivation.

Although Lewis and Clark found venereal disease very prevalent among the Chinooks and Clatsops who inhabited the region about the mouth of the Columbia River, the early explorers and fur-traders make no mention of it or of other diseases among the Oregon Indians, save smallpox. Robert Gray, in 1792, does not mention it, and Captain Bishop of the ship Ruby, who spent some time among the Chinooks in 1795 and described the natives in detail, does not refer to syphilis. Yet 10 years later it was widespread, and by 1814 had reached epidemic proportions among the fur-traders from their contact with native women. Undoubtedly syphilis and its companion, gonorrhea, were introduced by the crews of the fur trading ships that came in increasing numbers. Spread of these diseases was facilitated among the Clatsops and Chinooks, especially, by the low sexual standards of these tribes on which comment was made by virtually all of the earlier writers.

Regarding the Indians, Lewis stated that once contracted by them venereal disease continued during life, always ending in decrepitude, death or premature old age, although as he thought, from the use of certain plants, together with their diet they did not suffer great inconvenience. He regarded this as especially true among the Chippewa Indians, farther east, who used a decoction of lobelia and of a species of sumac. These decoctions were drunk in liberal quantities and were regarded by Lewis as effective both in syphilis and gonorrhea.

Under date of February 7, 1806, Lewis wrote that the smallpox had carried off a large number of natives near the mouth of the Columbia. The disease had prevailed 4 or 5 years earlier among the Clatsops and destroyed several hundreds of them. He regarded this epidemic as accounting for the deserted villages along the coast toward the Tillamook district.

During the stay of the party at Fort Clatsop the Indians frequently brought their sick to the captains for treatment. Many of the natives benefited from the medicines administered. One young Clatsop chief, cured of some ailment, brought his sister to Captain Lewis as a reward. The captain refused her, much to the chagrin of the chief as well as of the damsel, who after remaining about the door of Lewis's quarters for some time departed, as had the brother earlier.

The party began its homeward journey on March 23, 1806. It explored the Willamette River

as far as the present site of Portland, and continued eastward along the south bank of the Columbia. The large number of eye ailments among the Indians again impressed the leaders. Clark wrote on April 8, when the party was between the Sandy River and The Dalles, concerning an Indian woman who was blind in one eye, and of a man nearly blind in both eyes. He stated that blindness appeared to be more common among the natives of the Columbia than among any other people he had ever observed, and that they almost invariably had sore eyes at all ages, with the loss of one eye very common, and complete blindness almost invariable in old age. Clark, like others who commented on this affliction among the Columbia River Indians, was inclined to ascribe it to the reflection of the sun on the water to which the Indians were constantly exposed while fishing and to the fine sands carried by the wind. It is now known that trachoma was very prevalent among many Indian tribes. This disease no doubt caused the eye conditions which the explorers commented upon.

The contact with the white men the previous fall had evidently given the Indians along the Columbia a great deal of confidence in the medical ability of the captains. On April 28, between The Dalles and Walla Walla, Clark stated in his journal that several sick persons were brought to the captains for medical aid. One had a knee contracted by rheumatism, another had a broken arm, etc. All were treated, much to their gratification. They were given some eye water which Clark thought would be of more help to them than any other article the party could offer them.

They continued their search for answers to the questions concerning medical matters among the Indians. Lewis wrote on April 30 of trading one of their poorest horses for a very good one with a Chopunnish Indian. He commented on the practice of segregation of menstruating women from the remainder of the family. The daughter of this Indian, having arrived at the age of puberty, was obliged to sleep at a distance from her father's camp and when travelling to follow at some distance behind. At other camps of this Chopunnish tribe he observed a small lodge with one fire which served as a retreat for the women during menstruation. The men were permitted to approach no nearer than fifty to sixty paces from this lodge, and if they desired to convey anything to the occupants they would throw it toward the hut as far as they could and retire.

Clark wrote on May 5 of giving a native some volatile liniment to rub on his knee and thigh for pain. The Indian soon recovered and "has never ceased to extol the virtue of our medicine." The previous fall, near the Kooskooske River, an Indian had been encountered who could not walk because of a tumor on his thigh. Clark wrote on the return trip that he gave him a gentle purge, cleaned and dressed his sore and left him some castile soap to wash the sore, which soon got well. This man also credited the captain with curing him, the two cures having given the natives an exalted opinion of Clark's skill as a physician. They came to him in considerable numbers for relief from various ills. The captains considered it pardonable "to continue this deception," namely that they were skilled healers, for the Indians would not furnish any provisions without compensation in merchandise and the party's stock of goods by now was greatly reduced. Clark added that he and Lewis took care to give the Indians nothing which could possibly injure them, and that many times medical and surgical relief was afforded "in simple cases."

Lewis noted that scrofula, ulcers, rheumatism, sore eyes and the loss of use of their limbs were the most common types of ailments among the Indians of the Columbia. Regarding paralysis of the extremities he wrote that he had seen three instances among the Chopunnish. A chief of considerable note had been afflicted with it for 3 years, being incapable of moving a single limb and lying like a corpse in whatever position he was placed. Yet he ate heartily, assimilated his food, and was in a good state of nutrition. His pulse was good and he understood what went on about him. Lewis thought that the natives' diet of roots and other plants was in part responsible for some of their ailments.

While the party was on the upper Kooskooske River (in Idaho), Clark wrote on May 24 that one of his men (Bratton) was very low, eating heartily, but being so weak in the small of his back as to be unable to walk, although every remedy had been employed. One of the men stated that he had seen similar cases restored to health by violent sweats, so at the request of the patient this treatment was undertaken. A hot fire was made in a hole four feet deep and three feet in diameter, dug for the purpose. After burning long enough to thoroughly heat the ground, the fire was withdrawn, a seat was placed in the hole, the patient being placed thereon, with a board under his feet for protection. The hole was covered with blankets, supported by hoops, and a receptacle of water was handed the patient, with instructions to throw the water on the bottom and sides of the hole. After about twenty minutes in the steam-bath thus produced the patient was removed and

placed into cold water for a few minutes. He then was returned to the hole for about an hour, removed again and covered with blankets which were removed one by one until the man cooled off. The account concludes: "This remedy took place yesterday and Bratton is walking about today and is much better than he has been."

The Indians requested that the same treatment be applied to the paralyzed chief previously mentioned. The latter was so disabled that he could not sit up at the first attempt, but by arranging a system of thongs and guy ropes to support him, a second attempt was successful. He suffered some shock, and was given twenty drops of laudanum. The following day he could use his hands and arms. After several repetitions of the treatment he became able to use his legs and felt perfectly well. There is little in the description of either of these cases or their treatment to aid in diagnosis. Since the sweat-bath treatment was widely used by the Indians themselves in all parts of the continent, it could hardly have been new to this tribe in the Rockies, but perhaps the white man's modification of it and the results they had seen on Bratton caused them to have it tried on the chief.

On reaching the Bitter Root Mountains the party divided into two groups for further exploration and to recover supplies and canoes cached at different points on the westward journey. It was reunited on August 12, 1806, near the junction of the Yellowstone and Missouri Rivers, according to plan. Just before the two groups were joined, Captain Lewis was accidentally shot in the leg, while hunting, and for a time was seriously ill. Captain Clark was obliged to assume responsibility for the rest of the journey which was resumed on August 17, the party proceeding down the Missouri River. Five days after he was injured Lewis recovered sufficiently to be able to walk for the first time.

After crossing the continental divide and leaving the Oregon Country on the eastward journey, the medical notes, as well as notes on other matters, are scanty. The effects of contact with the luetic Mandan, Chinook and Clatsop women remained with some of the men, who were taken to the Great Falls of the Missouri for rest and treatment with mercury. This item and the wound received by Lewis constitute the chief entrees of medical interest. The party visited a few days with the Mandan Indians with whom it had spent the winter of 1804–05, and then continued the journey down the Missouri, reaching St. Louis on September 23, 1806.

The epochal journey, planned by the far-seeing Jefferson, and so important in establishing the claims of the United States to the Great West was brought to a successful conclusion with the loss by death of only one man. Judging from the simple narrative of the journals, the party faced a number of serious medical problems. Thanks to the hardiness of the men and the healthy life of the trail, supplemented by such stock of medical knowledge as the captains possessed, there is no indication of permanent disability, save of course the effects of venereal disease which must have remained with many of the men in spite of the drastic treatment employed.

REVIEWS OF NEW BOOKS

A CLEAR and concise presentation of facts is made in *Fundamentals of Clinical Neurology*[1] by Merritt, Mettler, and Putnam which will aid the student and the physician interested in neurology and its applications in the diagnosis of organic disturbances of the central nervous system.

A small and compact section deals with the examination of the nervous system in a rather rapid and cursive way. The intention of the authors was to expose a practical technique for examination of the patient from which all special and finer procedures have been omitted. However, a small chapter on the examination of a comatose patient seems to be too brief and may leave the examiner rather helpless.

The second portion of the book deals with the anatomic diagnosis of peripheral as well as central nervous system lesions. This is the most important portion and is beautifully presented with a large number of good, anatomical as well as schematic illustrations and photographs. In this presentation great emphasis is put on the structure of the various portions of the central nervous system and especially on their arterial blood supply and their venous drainage which is so commonly neglected in other books on clinical neurology and one remains conscious throughout the text of the cerebral and spinal cord blood circulation and its connections with the rest of the blood vascular system. Anatomic structure, blood supply, and function are closely associated, and the disorders arising from disturbances in this association are briefly but clearly mentioned and discussed. The chapters on spinal cord syndromes, spinal cord transections, diseases of the cerebellum, tumors of the brain, and vascular lesions of the brain are brief and give a rather incomplete picture of the symptomatology and the pathology associated with these lesions. The section on the anatomic diagnosis includes a chapter on peripheral nerve, dorsal root ganglion and ventral column cells, on the spinal cord, on the infratentorial brain stem, on the cerebellum, on the thalamus and corpus striatum, and on the cerebral cortex. The last chapter deals with the cerebral spinal fluid, its circulation, function, and composition, the methods of examination, indications and contraindications for lumbar puncture, measurement of pressure and testing of dynamics and also gives an excellent presentation of the pathologic changes seen in the spinal fluid and their diagnostic value. It gives a clear and complete summary of changes occurring in the spinal fluid in various types of cerebral and spinal cord lesions including trauma, meningeal infections, abscesses, bacterial infections, tropical diseases, hemorrhages, tumors, intoxications, and generalized diseases originating in other organs and involving the cerebrospinal fluid pathways.

This is a short and excellent book which should be read by all medical students and kept on the desk of most physicians. GEORGE PERRET.

THE author's purpose, as stated in the preface of *Color Atlas of Hematology*[2], is to furnish a color atlas of hematology for medical students, laboratory workers, and general practitioners of medicine. This the author has accomplished in a small book of 204 pages which is easily handled. In addition to the excellent color pictures and a brief description of each normal and pathologic cell type there is also a brief discussion of the hematologic features of various blood diseases with the typical blood picture of each disease. There are short chapters on blood parasites, the Rh factor, and bone marrow.

This book is not just an atlas. It also contains chapters on the more important hematologic techniques, on the normal standards of human blood, and on the blood picture of various laboratory animals. A unique aspect is the beginning chapter on definitions of hematologic terms and the last chapter on hematologic findings in various diseases and conditions arranged in alphabetic form.

Although the material in this book is, for the most part, taken from the author's larger work *Diseases of the Blood*, it is a concise and excellent atlas of hematology. It will be useful to technicians and medical students in the laboratory, and to clinicians in the diagnosis of blood diseases. OPAL HEPLER.

IN the volume *Curare; its History, Nature and Clinical Use*[3] the author presents an exhaustive and critical review of the surprisingly extensive literature on curare. As the author states it, "This book attempts to bring together the stories of the early explorers; the accounts of the botanists, whose search for the many and elusive plants used in the fabrication of curare is by no means concluded; the early investigations of the poisons on animals; the chemical examination of curares, which during the last ten years has progressed rapidly; and modern physiological and pharmacological research, culminating in the present extensive clinical use of the drug." The book is well written, the references are complete, and there is a full index. Physiologists, pharmacologists, and clinicians are greatly indebted to the industry and effort of the author for this source book of information and nonscientific laymen will find a wealth of interesting and instructive material in it. The book is timely in view of the renaissance of interest in the therapeutic uses of curare. With respect to this the author's comments merit quotation: "With the pioneer work of Griffith and the investigations of Cullen

[1] FUNDAMENTALS OF CLINICAL NEUROLOGY. By H. Houston Merritt, M.D., Fred A. Mettler, M.D., Ph. D., and Tracy Jackson Putnam, M.D. Philadelphia and Toronto: The Blakiston Co., 1947.

[2] COLOR ATLAS OF HEMATOLOGY; WITH BRIEF CLINICAL DESCRIPTIONS OF VARIOUS DISEASES. By Roy R. Kracke, M.D. Philadelphia, London, Montreal: J. B. Lippincott Co., 1947.

[3] CURARE; ITS HISTORY, NATURE, AND CLINICAL USE. By A. R. McIntyre, Ph.D., M.D. Chicago: The University of Chicago Press, 1947.

in anesthesia, curare became fully established as an important and useful adjuvant, and today the drug appears to be entering upon a period of trial in a wide variety of conditions. This phase is nearly always encountered with therapeutic agents, that is, after emerging from a period of neglect they pass through a period of overuse, and then the period of overenthusiasm is often followed by a period of reaction and disappointment. Hence it may be some years before the field of true usefulness of curare is finally evaluated." There will be less disappointment if those who plan to try curare for any purpose consult this authoritative volume. CARL A. DRAGSTEDT.

THE account of the isolation and application of folic acid to the macrocytic anemias presented by Dr. Spies in *Experiences with Folic Acid*[1] is a brief and readable corollary to the volume published last year on the biological aspects of the blood dyscrasias. As the author points out in his introduction, this important medical discovery was the result of work carried on in many different laboratories. Intimately associated as he has been, from the biochemical as well as the clinical viewpoint, Dr. Spies is admirably qualified to integrate and summarize the steps which have been accomplished toward an understanding of the pathogenesis and treatment of pernicious anemia and the related anemias.

The introduction is a simple but complete account of the breaking down of potent liver extract and the assay of its chemical constituents. It is followed by a chapter on selection of subjects and methods of study, which provides not only a fascinating account of experience with folic acid but a notable example of large scale clinical research excellently directed.

The studies were carried on in centers in Cincinnati, Birmingham, Havana, and San Juan, Puerto Rico. The criteria for the selection of patients were carefully defined and were adopted in all hospitals involved in the study, and the rules for management were rigidly adhered to. The response to folic acid is discussed on the basis of 78 cases of addisonian pernicious anemia, 76 of tropical sprue, 2 of nontropical sprue, 46 of nutritional macrocytic anemia, 3 of macrocytic anemia of pregnancy, 8 of nutritional leucopenia, and 5 of cirrhosis of the liver. Hemopoietic response was satisfactory in all cases except several of the cirrhosis group.

A pure synthetic substance has thus been found which causes regression of the symptom-complex associated with the macrocytic anemias and remission of the blood picture. There is slight evidence that it will prevent neural disturbances in pernicious anemia. EDITH B. FARNSWORTH.

THE four hundred and thirty page book *Diagnostic neuro-chirurgical* by Guillaume and Sigwald[2] is to our knowledge the first book on neurosurgical diagnosis published in France and written by two French neurosurgeons. Throughout its 430 pages, its authors stress the necessity of making an early diagnosis in order to perform an early operation before irreversible damage and changes have taken place in the cerebrum. Their main objective is to familiarize the practitioner with the diagnosis of neurological conditions which can be helped by surgery. They make him conscious that not only intracranial tumors need early operation, but that other neurologic diseases may benefit greatly from surgical intervention, diseases such as types of epileptiform seizures, hydrocephalus, acute cerebral hemorrhage, and certain neuralgias involving cranial and other nerves.

The first part of this book deals with the surgical anatomy, physiology, and pathology of the brain and a short, anatomical and histological study is made of the various intracranial tumors. The reaction of the brain to neoplasms and increased intracranial pressure is also presented. The second part deals with the symptomatology of the neurosurgical lesions of the brain and includes chapters on the generalized symptoms and the local symptoms produced by tumors and their effect on the various cerebral functions. Examination of the patient and the more important diagnostic procedures are briefly mentioned.

In the third part of the book, which is the most important, the authors study the clinical pictures produced by space occupying lesions in relation to their location and the nature of the lesion and discuss the diagnosis and the possible abnormalities found in radiographies, encephalographies, or ventriculographies of that region. A short chapter is devoted to the anatomical and clinical study of craniocerebral injuries and their complications and sequelae. Three chapters deal with the spinal cord and the peripheral nerve root. The anatomy and physiology of the spinal cord is briefly reviewed, mostly from a surgical point of view, and the syndrome produced by various types of lesions in relation to their location are explained in a short and concise presentation. The symptomatology, etiology, the clincial form and the various diagnostic problems of spinal cord compression are discussed with more detail. The last two chapters are dedicated to the study of nerve root compression and spinal cord injuries.

Operative techniques and methods are not discussed and are hardly mentioned but the danger of spinal puncture in cerebral tumors with increased intracranial pressure and in acute craniocerebral injuries is emphasized. The authors follow very strict indications for the performance of diagnostic procedures such as spinal punctures, air studies or myelographies. Most of the illustrations are schematic drawings; the pictures are few but they are well chosen and expressive. GEORGE PERRET.

THE aim of the book to set out concisely the principles of operative surgery with adequate detail has been admirably done in *Eye Surgery*[3] by H. B.

[1] EXPERIENCES WITH FOLIC ACID. By Tom D. Spies, M.D. Chicago: The Year Book Publishers, 1947.

[2] DIAGNOSTIC NEURO-CHIRURGICAL. By Jean Guillaume and Jean Sigwald. Paris: Presses Universitaires de France, 1947.

[3] EYE SURGERY. By H. B. Stallard, M.B.E., M.D. (Cantab.), F.R.C.S. (Eng.). Baltimore: A William Wood Book. The Williams & Wilkins Co., 1946. Printed in Great Britain by John Wright & Sons Ltd., Bristol.

Stallard. The book was written at sea, in military transports, and in camps amidst distractions and without access to the ophthalmic literature, which in places gives it an urgency and personal appeal that makes it less dogmatic than the usual textbook on surgery.

The repetition as to anesthesia and the instruments make the book appear as though each subject was prepared for a new group of associates.

One misses the frequent references to the names in the literature of the history and development of each operation, but each subject is taken up in the practical application of details under the harassing circumstances of war.

The introductory chapter discusses the operating room layout, staff discipline care and maintenance, medication, anesthesia, sterilization, general postoperative treatment, and dressings.

Much space is given for the general principles of plastic surgery and the operative technique for reconstruction of the lids after war injuries, and there is discussion of civil and military accidents.

The surgical anatomy is given in detail of each subject presented, and the possible complications emphasized in regard to the major and minor surgical procedures.

The use of diathermy and katholysis in the treatment of hemangiomatosis retinae as well as of retinal separation is given and the application of radon seeds for the treatment of glioma retinae and for malignant melanoma of the choroid. Illustrations are concise as are the details for the excision of a tumor of the choroid.

The author's results in statistical form with the operative procedures are included in the care of retinal separation, hemangiomatosis retinae, and of the use of radon seeds in malignancy.

It is an excellent book on surgery which is small enough that it can be easily carried about for quick reference and also gives the details for the eye surgeon who does not operate frequently.

BEULAH CUSHMAN.

IT is now twenty-two years since Professor Boyd first wrote his *Surgical Pathology* and during that time he has published six editions. The sixth edition,[1] which is now at hand, affords ample evidence for the long popularity of the book. Designed not for the professional pathologist, but rather for the practicing surgeon and the student who is preparing himself to take the examinations of the American Board of Surgery, this book is readable, comprehensive, and modern. Professor Boyd is well known for his lucid style, his wit, and his gifts as a teacher. Such qualities, which are all too rare in medical books, add greatly to the value of this one and to read it is a profitable experience.

New material includes a critical review of the etiology of cancer with discussion of Bittner's milk factor in relation to carcinoma of the breast, of avitaminosis in cancer of the mouth, and of Papanicolaou's vaginal smear method in diagnosing cancer of the cervix uteri. Because of the recent interest in the surgical treatment of certain congenital diseases of the heart an entirely new section has been added dealing with the pathological physiology of such lesions. Other new material includes a discussion of fibrous dysplasia of bone, inflammatory nodules of muscle in chronic arthritis, and fibrositis of the back.

WILLIAM B. WARTMAN.

AFTER a period of 5 years, a second edition of Duncan's extremely valuable volume on *Diseases of Metabolism*[2] has appeared. The chapters on special subjects are written by our leading authorities. They have been brought up to date, each chapter closing with a recent bibliography. The chapter on carbohydrate metabolism is by Professor C. N. H. Long and contains a clear and very complete exposition of the biochemistry of carbohydrate metabolism. That on protein metabolism is by Professor Abraham White with references to the newer work in electrophoretic studies of the plasma proteins as well as isotope studies of the intermediary metabolism of proteins. The chapter which deals with lipoid metabolism was also written by Professor White and is followed by 206 references many of them of the literature of 1945.

The review of the mineral metabolism is by Professor Cantarow. It covers pathological clinical conditions as well as physiological mechanisms. The chapter on water balance is by Professor Peters of Yale University and is very complete. There is an interesting article on the subject of the metabolic aspects of blood disorders by Dr. Tocantins which gives a comprehensive review of the metabolic aspects in hematology. The vitamins and avitaminosis are extensively reviewed and illustrated by Dr. Spies and Dr. Butt.

There is a chapter on undernutrition by Professor L. H. Newburgh of Ann Arbor. Obesity is covered very thoroughly, with explicit directions and many menus by Dr. Frank Evans.

Disturbances of intermediary metabolism, gout, diabetes, hyperinsulinism, are each covered by an outstanding authority. The present edition includes two new chapters. The diseases of the kidneys are described by Dr. Max Miller and Dr. Joseph M. Hayman, Jr., and disorders of the thyroid gland is a subject which is dealt with very completely and with comprehensive descriptions of iodine metabolism by Professor Alexander Winkler of Yale University.

This accumulation of modern and authoritative material on diseases of metabolism renders this volume one of great value to the student, interne, and surgeon who wish the last word on this subject.

PAUL STARR.

[1] SURGICAL PATHOLOGY. By William Boyd, M.D., Psychiat., M.R.C.P. (Edin.), F.R.C.P. (Lond.), L.L.D. (Sask.), M.D. (Oslo), F.R.S.C. 6th ed. Philadelphia and London: W. B. Saunders Co., 1947.

[2] DISEASES OF METABOLISM; DETAILED METHODS OF DIAGNOSIS AND TREATMENT. Edited by Garfield G. Duncan, M.D. 2nd ed. Philadelphia and London: W. B. Saunders Co., 1947.

THE concise, well edited, methodical *Year Book of Neurology, Psychiatry and Neurosurgery*[1] brings in 790 pages a good summary of the important publications on neurology, psychiatry, and neurosurgery published during the years of 1945 and 1946. Numerous important articles published in foreign countries have also been abstracted and broaden our contact with the great schools of Europe and South America.

The section on neurology emphasizes certain new acquisitions of knowledge of neuroanatomy and physiology. Numerous articles on the effect of new drugs on convulsive seizures such as tridione have been abstracted. A special place is given to the therapeutic effect of streptomycin, penicillin, and the sulfonamides on the various types of meningeal and cerebral infection. Also the use of penicillin in neurosyphilis is widely discussed. The chapters on disorders of the cerebrovascular system and cerebral infection and intoxication show the great importance placed on the studies of these disorders.

The section on psychiatry includes a chapter on child psychiatry, schizophrenic reactions, toxic psychosis, psychosomatic disorders, military psychiatry and therapy. Interesting articles are abstracted on the psychiatric complications of tropical diseases malaria, poliomyelitis, chronic inflammation of the central nervous system, head injuries, tuberculosis, and various other intoxications. Other articles deal with the psychiatric factors in duodenal ulcers and other gastrointestinal disorders and their treatment. The psychiatric aspect of various skin affections is also well presented. The last chapter deals with numerous articles on shock therapy, its physiologic basis, its effects and complications, the use of various drugs, and some reports on the result of prefrontal lobotomies in psychiatric disorders.

For the first time, a separate section in this year book is given to neurosurgery. As a direct result of research stimulated by the war and of war casualties, an increasing number of articles published in the past year deal with nerve injuries and craniocerebral injuries and their treatment. The use of sulfonamides and penicillin has greatly reduced the instances of infection of intracranial wounds and has altered the methods of treating them and also of treating brain abscesses. Various types of peripheral nerve lesions and their treatment are discussed. Numerous articles also are related to the complications of peripheral nerve lesions, such as causalgia, phantom limb pain and related painful syndromes, and the various ways of treating them are presented. Other chapters deal with sympathetic surgery, the surgery and the diagnosis of herniated intervertebral discs and related myelopathies and spinal injuries. A few articles on intracranial vascular lesions and intracranial tumors are also abstracted. A new hemostatic agent, gelatin sponge, other new therapeutic methods, and operative procedures have found their important place in this book which is invaluable for the busy and interested physician who does not always have the time to read the various and numerous specialized publications published all over the world.

GEORGE PERRET.

[1] 1946 YEAR BOOK OF NEUROLOGY, PSYCHIATRY AND NEUROSURGERY. Edited by Hans H. Reese, M.D., and Mabel G. Masten, M.D. for the section on Neurology; by Nolan D. C. Lewis, M.D., for the section on Psychiatry; and by Percival Bailey, M.D., for the section on Neurosurgery. Chicago: The Year Book Publishers, 1947.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

A HANDBOOK FOR THE DIAGNOSIS OF CANCER OF THE UTERUS BY THE USE OF VAGINAL SMEARS. By Olive Gates, M.D., and Shields Warren, M.D. Cambridge, Mass.: Harvard University Press, 1947.

THE ROTUNDA HOSPITAL, 1745–1945. By O'Donel T. D. Browne, M.B., M.A., M.A.O. (Univ. Dub.), F.R.C.P. (I.), F.R.C.O.G. Baltimore: Williams & Wilkins Co., 1947.

A TEXTBOOK ON PATHOLOGY OF LABOR, THE PUERPERIUM AND THE NEWBORN. By Charles O. McCormick, A.B., M.D., F.A.C.S. 2nd ed. St. Louis: The C. V. Mosby Co., 1947.

ASPETTI DI PATOLOGIA PLACENTARE; CON PREFAZIONE DI LUIGI BACIALLI E ARMANDO BUSINCO. By Massimo Mac iotta. Bologna: Nicola Zanichelli, Editore, 1947.

THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY. A COMPLETE DICTIONARY OF THE TERMS USED IN MEDICINE, SURGERY, DENTISTRY, PHARMACY, CHEMISTRY, NURSING, VETERINARY SCIENCE, BIOLOGY, MEDICAL BIOGRAPHY, ETC., WITH THE PRONUNCIATION, DERIVATION, AND DEFINITION. By W. A. Newman Dorland, A.M., M.D., F.A.C.S. 21st ed. Philadelphia and London: W. B. Saunders Co., 1947.

RECONSTRUCTIVE AND REPARATIVE SURGERY. By Hans May, M.D., F.A.C.S. Philadelphia: F. A. Davis Co., Publishers, 1947.

1946 TRANSACTIONS OF THE AMERICAN SOCIETY FOR THE STUDY OF STERILITY. Portland, Oregon: The Western Journal of Surgery Publishing Co., 1946.

SURGERY OF THE AMBULATORY PATIENT. By L. Kraeer Ferguson, A.B., M.D., F.A.C.S. 2nd ed. Philadelphia, London, Montreal: J. B. Lippincott Co., 1947.

FUNDAMENTALS OF PSYCHIATRY. By Edward A. Strecker, M.D., Sc.D., LL.D., Litt. D., F.A.C.P. 4th ed. Philadelphia, London, Montreal: J. B. Lippincott Co., 1947.

THE REHABILITATION OF THE INJURED. Vol. 2: REMEDIAL GYMNASTICS. By John H. C. Colson. London, Toronto, Melbourne, and Sydney: Cassell & Co., Ltd., 1947.

TRICHOMONAS VAGINALIS AND TRICHOMONIASIS. By Ray E. Trussell, M.D. Springfield, Ill.: Charles C Thomas, 1947.

CORRESPONDENCE

PLASMA CLOT GRAFT OF PERITONEUM FOR PERFORATIONS OF STOMACH

To the Editor: May I comment briefly on the article entitled "Plasma Clot Graft of Peritoneum for Perforations of Stomach" by Dr. Joseph Bloom which appeared in the August, 1947 number of SURGERY, GYNECOLOGY AND OBSTETRICS? Dr. Bloom used 9 dogs in his experiments, 4 of which survived. He explained the failures on the basis of mechanical defects in the technique of applying the grafts, rather than as being due to digestion by the gastric juice, and this in spite of the fact that digestion was described in the protocols of some of his experiments.

It is my feeling that no graft of tissue can be used to close a defect in the stomach wall successfully unless something is done to protect the graft from the action of the gastric juice. Price and Lee[1] have recently shown that virtually all living tissues, when used as implants in the stomach wall, are subject to digestion by the gastric juice and that the rate of digestion is greatly speeded up in the hyperacid stomach.

Neuhof[2] in 1917 attempted to repair defects in the stomach by the use of living fascia. In all instances the implanted fascia was digested by the gastric juice and perforation occurred. He found, however, that if gastroenterostomy was also performed, perforation was prevented and satisfactory healing ensued.

In 1929, I[3] published the results of experimental work in which I used alcohol preserved ox fascia lata to repair defects in the stomach wall. In my early experiments, perforations did not occur and I wondered if alcohol preserved fascia was more resistant to gastric juices than living fascia. This, however, did not appear logical as there was no reason for believing that the collagen fibers of the connective tissues were altered either chemically or physically by preservation in alcohol. I did not have to wonder about this long because in the next cases in the series the fascia in each instance became perforated due to digestion. I then did 5 cases in which I was able to prevent digestion of the implant by giving the dogs 3 ounces of bismuth subnitrate by stomach tube on the operating table as soon as the defect in the stomach was closed and then giving them 1 ounce daily in milk for the following 2 weeks. The bismuth probably protected the implant from gastric juice by forming a mechanical coating over it.

In view of the experiments of Neuhof, Price and Lee, and myself, I do not see how Dr. Bloom can expect his peritoneal grafts to be successful as a routine procedure. Price and Lee have shown that white fibrous connective tissue is one of the most resistant of living tissues to the action of gastric juice. In spite of this, Neuhof's fascial implants were all digested unless he diminished the action of the gastric juice by performing a gastroenterostomy. Some of my implants of preserved ox fascia lata were digested and some were not. Apparently they could be protected as a routine by giving large doses of bismuth subnitrate. Certainly the experimental work already done is discouraging for the use of any tissue as an implant to repair a defect in the stomach wall. If the implant does remain intact, however, the ultimate result is excellent. In my successful experiments, the implant became covered on the outside with glistening peritoneum with very few omental adhesions attached. The inside of the implant became covered with gastric mucosa which was perfectly normal in appearance.

I do not believe that oxycellulose gauze, used as a plug on the inside of the graft by Bloom in some of his experiments, could be counted upon as a routine to protect the graft from the action of the gastric juice. Oxycellulose gauze implanted among living tissues soon becomes a mushy mass (unpublished experiments of my own) incapable of protecting a graft from the action of the gastric juice until the gastric mucosa could have time to grow across it.

Baltimore, Maryland. AMOS R. KOONTZ.

[1]Price, P. B, and Lee, T. F. Surg. Gyn. Obst., 1946, 83: 61-72; ibid., 1947, 84: 959-961.
[2]Neuhof, H. Surg. Gyn. Obst., 1917, 24: 383-427.
[3]Koontz, A. R. South. M. J., 1929, 22:417-422.

THE PLASTIC SURGICAL CLOSURE OF DECUBITUS ULCERS IN PATIENTS WITH PARAPLEGIA

To the Editor: In the September issue of SURGERY, GYNECOLOGY AND OBSTETRICS, pp. 321–332, an article entitled "The Plastic Surgical Closure of Decubitus Ulcers in Patients with Paraplegia" appeared under my name and that of several of my assistants at the Veterans Hospital, Bronx, New York. Apparently I did not conform to the procedure of the Veterans Administration in that I failed to obtain permission of the Chief Medical Director of the Veterans Administration to publish this article.

Information has come to me that the Chief Medical Director has given his permission and that there is a standard footnote which should be published under such article. This footnote reads as follows:

"Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veteran's Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors."

New York, New York HERBERT CONWAY.

Fig. 2.

Fig. 5a.

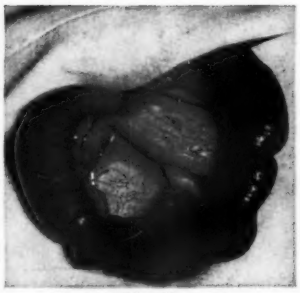

Fig. 6a.

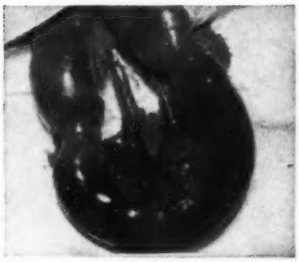

Fig. 3.

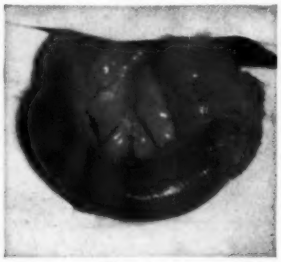

Fig. 5b.

Fig. 6b.

Fig. 7a.

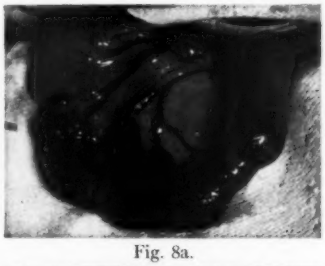

Fig. 8a.

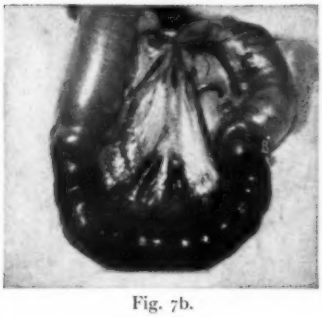

Fig. 7b.

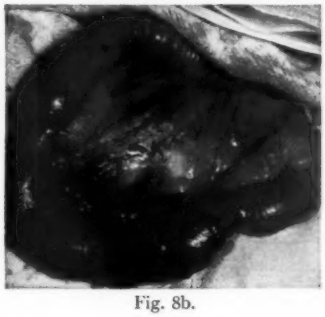

Fig. 8b.

The Rôle of Vascular Spasm in Recovery of Strangulated Intestine.—Harold Laufman and Harold Method.

UNIV. OF MICH.